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INTRACRANIAL MENINGIOMAS, SURGICAL RESULTS

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BETWEEN January 1, 1936, and January 1, 1947, one thousand and one brain tumors were verified in the Neurosurgical Clinics of the University and Postgraduate Hospitals of the University of Pennsylvania. Of these, 149, or 14.8 per cent, were meningiomas. Our interest is in this group. Although a review of this series of meningiomas at this time can show little of importance with regard to the ultimate life expectancy in many cases, nevertheless, certain other facts of interest will appear. Furthermore, this is not the record of a single operator. The majority of these patients were operated upon by the author, but his associates, assistants, and residents also contributed. Hence, this series represents what can be done in a neurosurgical clinic, every member of which is expected, eventually, to be sufficiently expert to remove a brain tumor.

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SURGICAL ASPECTS

Intracranial surgery has seen much technical improvement in the past 25 years. The development of ventriculography by Dandy made correct localization of the position of the tumor possible in over 90 per cent of cases. Electrosurgical methods, as introduced by Cushing (1), vastly improved hemostasis, of particular importance in attacking a tumor of the type under present consideration. From Cushing's clinic came the first description of the importance of suction in intracranial procedures (4), although Frazier had already used it for 2 years in operations on the trigeminal root. As the technique for intravenous transfusions was improved, the neurosurgeon rapidly appreciated its value, using, at first, saline alone, then adding blood if necessary and, finally, in this clinic at least and certainly in many more, routine whole blood transfusion in any intracranial procedure. Neurosurgeons have learned by hard experience how to handle increased intracranial pressure and all that it

Fig. 1. A.R., female, aged 45 years. Meningioma of left frontoparietal area; weight, 175 grams. Operation was performed December 27, 1945. Removal was complete. Patient was returned to previous occupation February 15, 1946. She was re-examined August 15, 1946, and March 15, 1947. Apparently she has made a complete recovery.

Fig. 2. H.E., male, aged 63 years. Meningioma to illustrate invasion of dura. The underlying tumor and overlying bone were completely removed; weight 140 grams. Operation was performed November 6, 1941. The dural defect was repaired with fascia lata. On June 1, 1944, patient reported with draining sinus of right frontal area. Exploration and removal of wax produced healing. January 15, 1947, patient was reported as completely comfortable. He was retired from business, on pension.

Fig. 3. A.B., male, aged 41 years. Meningioma left frontoparietal area; no record of weight. Operation was performed October 22, 1940. He reported December 13, 1944. He has had six right Jacksonian convulsions beginning in leg. He vacillates; judgment poor; starts a job but never finishes it. He has very slight right hemiparesis and spasticity. He was put on phenobarbital. On January 15, 1947 his condition was unchanged; he has had two more fits. He is unemployed.

Fig. 4. S.M., male, aged 31 years. Meningioma of right frontal area; weight, 185 grams. Removal was complete with upper edge of bone flap. Operation was done December 1, 1941. He returned to work April 1, 1941. He reported January 15, 1943. He had had generalized convulsions, 2 in past month. He was put on phenobarbital. Convulsions continued every 6 to 8 weeks. The cranial defect was repaired by cranioplasty April 5, 1944. He reported October 12, 1946. Neurological examination was negative. The convulsions continue. He is unemployed.

implies, before, during, and after operation. Ventricular tap will produce relief from intracranial tension just prior to operation thus materially reducing bleeding from the skin flap. Any tendency of the brain to herniate after the dura is opened is diminished, and the ease of tumor exposure and removal thereby increased. Wiring the bone flap, silk sutures, possibly deep and always superficial rubber tissue drains in all craniotomy wounds keep the flaps flat and safe. But in this clinic, tap of the lateral ventricle after intracranial surgery is the chief reliance in reducing postoperative tension within the skull. A patient suspected of having an intracranial mass lesion is very rarely operated upon without air studies, preferably, of course, a ventriculogram. Parieto-occipital burr holes for ventricular tap, usually bilateral, are inserted in every instance. Through these perforations, ventricular tap can be done for relief of pressure, preoperatively or postoperatively, and ventricular estimation or ventriculography carried out. The fact that only three tumors in this series were not surgically exposed at the first operative procedure is fair evidence of the value of such studies.

Proper supportive measures during the operative period are essential. Intravenous saline has been used routinely in this clinic since 1925. Now, every patient is given at least 500 cubic centimeters of blood. This transfusion is completed just before the bone flap is replaced, so that any consequent rise in blood pressure will produce oozing which the operator can check before the wound is closed. But one postoperative clot requiring re-elevation of the bone flap occurred in this series, fortunately with recovery. In another case, a clot was found at autopsy and considered to be of sufficient size to have been a factor in the fatality. Since autopsy was performed on every case in which a fatality resulted, this record can be substantiated. In but 6 cases was a two stage operation considered necessary; 1, a bilateral frontal 350 gram meningioma in a 14 year old boy, and another, a 250 gram meningioma of the left occipital pole in a 31 year old woman. It is our practice to turn down rather larger flaps than is customary in other clinics (see Fig. 6, d). This fact, plus the routine use of preoperative air studies, has made prompt and complete exposure of the tumor possible. In 8 cases bilateral frontal flaps were fashioned where an olfactory groove meningioma was suspected preoperatively to involve both sides of the falx.

VITAL STATISTICS

Of these 149 patients, 92 were females; 57, males. Four of the males and 2 of the females were negroes. The youngest patient was 2 years; the oldest, 76. The average age at operation was 43 plus years for the women, 43 minus years for the men. The average duration of symptoms prior to operation approximates 2¾ years. If 6 patients with preliminary seizures existing for over 8 years prior to operation are excluded, the preoperative period at which clinical evidence of intracranial involvement appears is just a fraction over 2 years. Injury appears to have been a factor in 14 cases, all vault tumors.

POSITION OF THE TUMOR

In his recent monograph, Cushing (2) has gone into great detail in describing the exact position and point of origin of each tumor in his series. We have attempted a similar accuracy in describing the position and point of origin, except in those tumors arising from the sphenoid ridge. The exact point of attachment of a tumor to the ridge or whether it arose from the pterion has been difficult to determine in most instances, even after careful examination of the preoperative x-ray films and a painstaking perusal of the always detailed operative notes. This group has simply been listed, therefore, as sphenoid ridge tumors. Possibly some of the meningiomas described in this series as olfactory groove tumors may have originated from the inner end of the sphenoid ridge. In operating upon meningiomas in this locality, especially when the tumors are bilateral, the author has always been too harassed by the technical difficulties to be very certain in every case of the exact origin of the tumor. Figure 5 gives the various locations of the tumors with the surgical results. As was to be expected, the more closely the tumor lay to the carotid vessels, olfactory groove, suprasellar area, sphenoid ridge, and

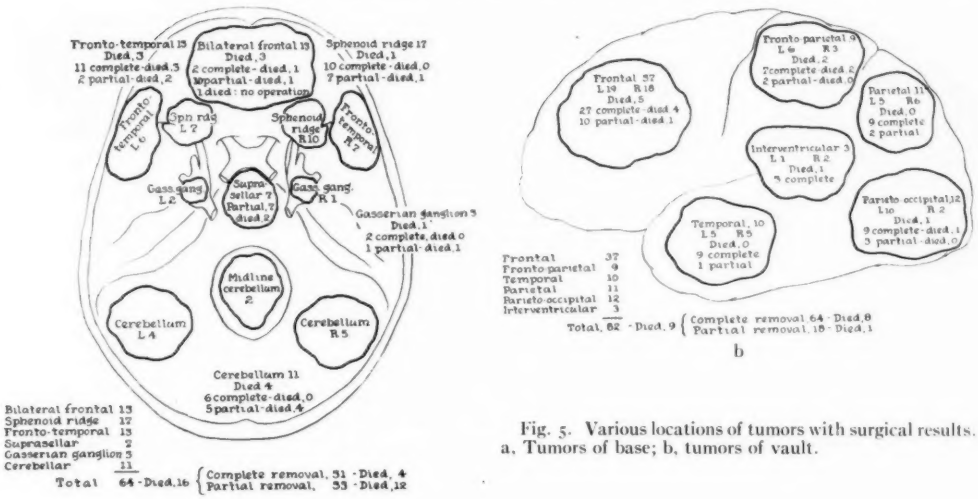


Fig. 5. Various locations of tumors with surgical results. a, Tumors of base; b, tumors of vault.

to the base of the skull, gasserian ganglion and posterior fossa, the higher the mortality and the less the chance of a complete removal. The surgical difficulties here are mechanical and inherent in the position of the tumor. In a second group of cases, the tumor lies in the convexity of the brain and is relatively easy of access. Success or failure depends on the operator's judgment, his opinion as to the patient's condition as a good or bad risk, and how much surgery is advisable.

In the first group were 64 cases with 16 deaths, a case mortality of 25 per cent; in the second, 82 cases with 9 deaths, a case mortality of 10 per cent. In the cerebellar group of 11 cases, 7 were removed, 4 completely and 3 incompletely, with recovery. Four died; 1, because the tumor lay in the vermis of the cerebellum and was never exposed (see Fig. 7, b) one, due to pontine softening following removal of the tumor; one, from pneumonia in a patient who stopped breathing preoperatively and was revived by an emergency ventricular tap; and the last, in an elderly man shown by neurologic study to have a large tumor involving all his cranial nerves from the fifth to the twelfth on the right. Radiologic studies showed a large defect in the bone. A chordoma was suspected but, since he had intense trigeminal pain, a medullary tractotomy seemed indicated. This was performed and the tumor simply verified, without attempt at removal.

TABLE I.—POSITION OF TUMOR IN 34 CASES WITHOUT POSTOPERATIVE SEQUELAE

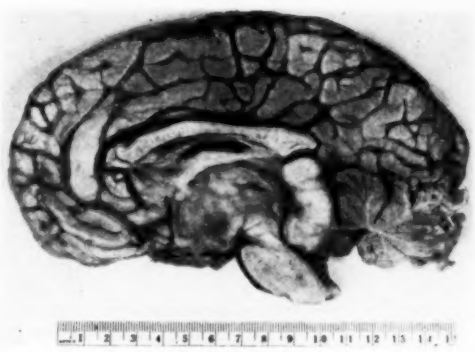
Bilateral frontal	13	No PO symptoms	3	partial removal 2; 4, 4 yrs. complete removal 1; 2 yrs.
Sphenoid ridge	17		2	complete removal 2, 2 yrs.
Frontal, left and right	37		13	complete removal 10, 10, 10, 10, 10, yrs. 7, 6, 5, 4, yrs. 3, 3, 3 yrs. 2 yrs.
Temporal	23		3	complete removal 10, 6, 5 yrs.
Parietal	32		6	complete removal 7, 7, 7 yrs. 6, 5, 3 yrs.
Cerebellar	11		3	complete removal 7, 7, 6 yrs.
Suprasellar	7		1	incomplete removal 7 yrs.
Gasserian ganglion	3		2	complete removal 2, 2 yrs.
Interventricular	3		1	complete removal 5 yrs.
	146 cases	Total	34 cases	

Fig. 6. Meningioma-characteristic vascular groove changes in bone, operative specimen, and operative scar. a, Enlarged vascular markings in skull over meningioma. b, Flap replaced postoperatively with area of bone involved in tumor burred away. c, Tumor removed. Weight 180 grams. Note nodular appearance and complete encapsulation. d, Patient to show left frontoparietal flap and burr hole for ventricular tap.

Atelectasis of the right lower lobe developed with death from pneumonia in 6 days. Both of the deaths in the group of suprasellar tumors were accompanied by hyperthermia. Autopsy in each case showed only partial removal of a tumor which extended backward to involve the third ventricle. In the group of 13 bilateral frontal or olfactory groove meningiomas, the cause of 1 death was inanition and chloride deficiency on the forty-second day, following the removal of a 375 gram tumor in two stages, from a 14 year old boy. The second death occurred from presumed operative shock within 24 hours, following partial removal of an olfactory groove tumor from a 54 year old woman who was a good preoperative risk. The third death, in a 47 year old woman in excellent physical condition, was

a

c



b

Fig. 7. Autopsy specimens of 3 meningiomas in this series which were not discovered at operation. a, Tumor *en plaque* on left side of falx. Tumor not exposed because operator failed to explore close to midline. b, Midline tumor involving cerebellar vermis. Tumor believed to lie in cerebellopontine angle. Unilateral suboccipital approach failed to reveal widening of cerebellar vermis. c, Diagnosis in this case was brain abscess in right temporal lobe. Tumor found at autopsy. Relation between a tumor along sphenoidal ridge and adjacent carotid is clearly shown.

due to rupture and prompt control by clipping of the right internal carotid artery. The attack on this tumor was conducted in two stages, blood loss was never a serious factor, but she developed a complete left hemiparesis, never recovered consciousness and died in 48 hours. Autopsy showed no postoperative hemorrhage and no pulmonary or cardiac involvement. On 5 other occasions, in tumors unconnected with this series, a clip has of necessity been applied to the right internal carotid during an operative session. Three of these patients recovered, although the left hemiparesis and hemianopsia were, unfortunately, complete and permanent.

Among the 5 deaths in the frontotemporal group, the first occurred in a 53 year old woman, 14 days following partial removal of a tumor in the left sylvian fissure, and the second from surgical shock, 2 hours after removal of a 168 gram meningioma from the right sylvian area in a 52 year old woman who was an unfavorable risk. This death was due to bad surgical judgment, as a one stage rather than

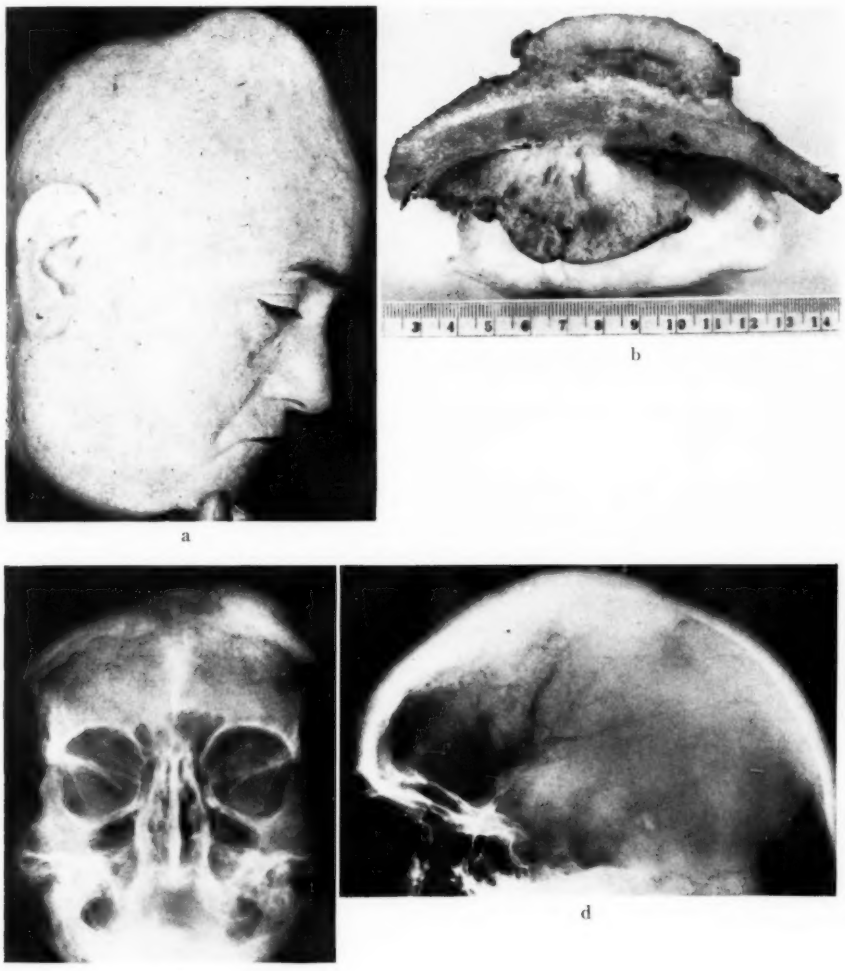


Fig. 8. To illustrate typical findings in meningiomas. a, Patient with frontal exostosis of skull. b, Transection of specimen removed to illustrate involvement of bone, dura, and brain by meningioma. c and d, Frontal and lateral craniograms to show characteristic bone changes.

a two stage procedure was used. The third death occurred 6 days postoperatively from meningitis, the only case in this series from this cause. The fourth fatality took place in a 47 year old woman with uncinate fits. Fifty-five grams of a meningioma, lying in the floor of the right middle fossa, were scalloped out with the bovie. Autopsy 5 days later showed 60 grams more of tumor remaining and extending down through the incisura into the right cerebellopontine angle. The fifth mortality resulted from pneumonia 5 days after the removal of an 80 gram tumor from the left middle meningeal area of a 60 year old male. He was a poor risk, sent in from a neighboring asylum, where, because of his aphasia and

a b

Fig. 9. Typical ventriculogram. Meningioma close to falx, left cerebral hemisphere. Figure 3, frontispiece, shows this particular tumor exposed. a, Anteroposterior; b, lateral.

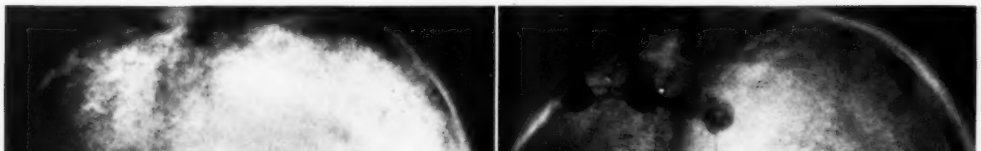
mental dullness, a diagnosis of senile arteriosclerosis had been reached. No great technical difficulty or hemorrhage attended the removal of this tumor. The patient was semiconscious with stertorous breathing when first seen and was considered an emergency. But he was a recent case, plenty of blood was available, surgical shock was never a factor, and he should not have died.

The single mortality in the three gasserian ganglion tumors occurred in a patient who was operated upon as a suspected case of trigeminal neuralgia involving the second and third divisions on the left. The tumor was found and partially removed. She died of meningitis on the third day. Autopsy revealed an unsuspected right frontal abscess leaking into the ventricle.

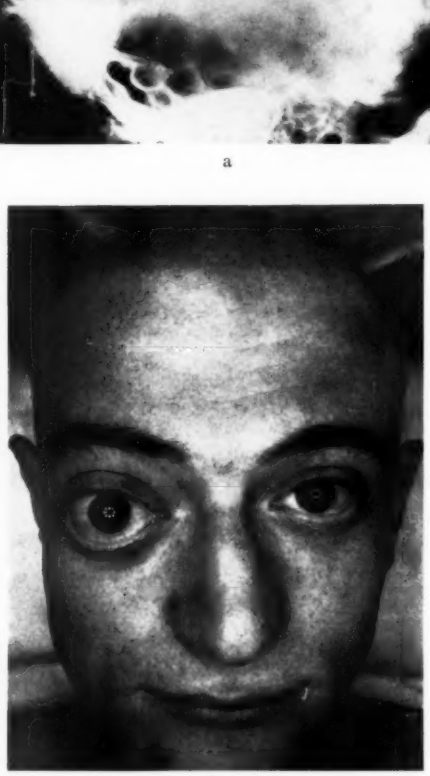
The second group of tumors in this series is made up of those tumors lying over the convexities of the brain, away from the base. There are 82 cases in this series, with 9 deaths, roughly a 10 per cent case mortality.

The first of these was a tumor lying in the posterior frontal area attached broadly to the falx. The patient was a good operative risk. He had a convulsion on the table and one immediately after operation. He died in 72 hours from respiratory difficulty. Autopsy showed that he had a myxolipoma of the epiglottis which seemed sufficiently large to have been the cause for his respiratory embarrassment. Furthermore, he had aplasia of his right kidney. The operative wound was clean and the tumor had been completely removed.

In the second case, a 47 year old woman, definitely a bad surgical risk, died 10 days after a second stage removal of a 150 gram meningioma from the left frontal area. This tumor was attached to the dura over the convexity only and not to the falx. Autopsy showed a bilateral bronchopneumonia with enough old clot in the operative site to raise a definite suspicion that postoperative hemostasis had not been adequate. In the third case, a 40 gram meningioma, lying fully *en plaque* against the falx in the median fissure, was completely overlooked following exposure of this area (see Fig. 7, a). The patient died in 24 hours from increased pressure and autopsy revealed the tumor. This is 1 of the 3 cases in this series in which the tumor was not found at operation. The fourth fatality occurred in a 52 year old woman from whom 170 grams of meningioma had been removed from the right temporal area. This tumor was attached to



a c



b

Fig. 10. a, Roentgenogram to show bony thickening by tumor in this area. b, Face view of patient with unilateral exophthalmos caused by meningioma involving sphenoid ridge and orbital plate. c, Postoperative film to show apparently complete operative removal of tumor.

the dura alone and not to the falx. The patient was not a good operative risk and the operator used poor judgment in attempting to remove the tumor at a single sitting. The patient died 2½ hours later, obviously from surgical shock. The last of these frontal fatalities occurred in a 67 year old woman who was obese, hypertensive and had evidence of cardiorenal disease. A 32 gram meningioma, attached to the dura, was easily removed. The patient made a good immediate postoperative recovery, but died suddenly 2 weeks later from abrupt cardiac failure.

One of the 2 cases in the parietal group was a 39 year old woman who was a good operative risk. A 200 gram meningioma was found in the parietal area, attached to the dura only. An attempt to remove this lesion at one stage resulted in an immediate death on the table, from operative shock. The second death occurred in a 62 year old woman with an exostosis of the left frontoparietal area. The exostosis, plus a small meningioma *en plaque*, was readily removed (see Fig. 8, a, b, c, d). The patient made a good postoperative recovery, but died suddenly 17 days after operation as she was dressing to go home. Autopsy showed a pulmonary embolism. The wound was clean.

Two fatalities followed removal of a meningioma in the occipital area. The first of these was a 56 year old woman with a heart murmur and a uterine myoma. An 80 gram meningioma was successfully removed from the right occipital region. She died on the seventh day from bilateral bronchopneumonia and cardiac failure. Autopsy showed that the wound was entirely clean. The second death was in a 29 year old woman, 6 months pregnant, and a fair operative risk. An 80 gram meningioma was removed from the body and posterior horn of the left lateral ventricle. At the end of 48 hours the patient seemed to be in

good condition, but died suddenly about 60 hours after operation, apparently from abrupt cardiac failure. Autopsy showed the wound clean and the tumor completely removed.

In addition to these 25 operative deaths, there were 3 other cases verified as meningioma in which no operation was performed. In one case, a 55 year old woman, blind, deaf, and aphasic, was refused operative intervention. Autopsy showed 175 grams of tumor springing from the left sphenoid ridge and filling up the left sylvian fissure. The second case was a 64 year old woman, totally blind and anosmic for 3 years, with complete bilateral optic atrophy and x-ray evidence of marked sellar erosion. She too was considered to have an inoperable lesion. Autopsy showed a large, bilateral olfactory groove meningioma. The third case was a 42 year old woman who was admitted because of pain in and behind her right ear and a story of a chronic draining ear for 30 years. She was mentally dull with a right-sided headache. Lumbar puncture showed 9100 white blood cells in the spinal fluid. X-ray studies showed a sclerosing and destructive process in the right mastoid together with questionable erosion of the right sphenoid ridge. Tap was made for a right temporal lobe abscess without success, and a mastoidectomy revealed chronic mastoiditis. She died from increased pressure about 48 hours after mastoidectomy. Autopsy revealed a large meningioma involving the right sphenoid ridge and weighing, roughly, 160 grams. The right anterior and middle cerebral arteries were involved (Fig. 7, c).

PATHOLOGY

Our studies on the subgrouping of these cases are incomplete. The publication of Cushing's superb monograph on the meningiomas opened up many new pathologic vistas involving this particular group of neoplasms. But although his classification has been applied in the microscopic study of these tumors since 1941, time has not permitted a complete review of the 1936-1940 cases. This review has been undertaken and will be presented in the near future. Suffice it to say here that the pathologic diagnosis of each of these cases has been made and is simply meningioma, without any attempt to classify them further.

DIAGNOSIS

In 33 of these 149 verified meningiomas, localization of the lesion was impossible on the basis of careful and painstaking neurologic studies and routine x-ray examinations. It must be admitted that 11 of these patients were stuporous or unco-operative, so that detailed neurologic examinations, including particularly visual fields, could not be made. In every case proper localization was made by ventriculography (see Fig. 9, a and b). The tumor was exposed and completely or partially removed in 32 of these 33 cases. The only case in which the tumor was not exposed was in that instance where it lay in the cerebellar vermis in the posterior fossa. In a second case, already mentioned, the patient was suspected of having a right temporal lobe abscess, the presence of a right sphenoidal ridge meningioma being revealed only at autopsy. No air studies were carried out in this case.

In the remaining 115 cases, the location of the lesion was obvious either from detailed neurologic examination, including, of course, careful study of the visual fields, or from the flat x-ray plate. Inasmuch as these tumors are known to originate from the envelopes of the brain, and consequently affect its surface, it is of interest that of the 70 tumors, frontal, temporal and parietal, which, from their position, might affect either the motor or sensory cortices and produce either motor or sensory focal convulsions, in but 21 of these 70 cases were focal convulsions recorded. Fifty-nine of these 70 cases, however, showed a contralateral motor loss or pathologic reflexes indicating pyramidal tract involvement.

With regard to the other means of diagnosis and localization, flat x-ray films were entirely negative in 48 cases. In 81 cases flat x-ray films strongly suggested the position of the lesion and in 38 of these, not only was the position of the lesion correctly estimated but a positive diagnosis of meningioma was reached. In 10 instances the x-ray reports (see Fig. 6, a; Fig. 8, d and c; Fig. 10, a) were entirely misleading as to the position of the tumor. In 20 cases the presence of a mass lesion was definite on the basis of the pineal shift. In the 48 cases in which an initial study of the flat plate was reported as negative, restudy of the plate, af-

ter the position of the tumor was known, showed suggestively positive findings in 14. Ventriculograms (see Fig. 9, a and b) were performed in 61 cases with 2 missed diagnoses, both because of insufficient air. In one of these instances, exploration on the basis of reasonably positive neurologic signs revealed a tumor. In the second case, a repetition of the ventricular studies proved to be positive. A ventricular estimation was performed in 31 instances and in each case proved confirmatory of the position of the tumor, already fairly well established by other means.

In 20 instances an encephalogram was carried out, localizing the tumor accurately in 16 cases, with 4 failures. In these 4 cases, ventriculographic studies cleared up the situation.

Electroencephalography has not been used extensively in this clinic. In this series of cases, 13 electroencephalographic studies were made, with 11 positive and 2 incorrect diagnoses.

In 3 instances an arteriogram was used, once under the suspicion that we were dealing with an aneurysm, and this lesion was ruled out by the arteriogram. In the second case the arteriogram was performed on the wrong side with negative results, and in the third case it was positive for the presence of a tumor.

The weight of these tumors may be of interest because it gives some clue as to their size (see Fig. 6, c). Two of these tumors weighed over 300 grams; 4, over 200 grams; 14, over 150 grams; 15, over 100 grams; 26, over 50 grams; and 14, 25 to 50 grams. The average weight of the 75 tumors in which it was recorded was 108 grams.

SURGICAL CONSIDERATIONS

In meningiomas, owing to the very slow growth of the tumor, the patient's physical condition is usually better than when the brain has been invaded by the more rapidly expanding gliomas. Inanition from continuous vomiting is less commonly seen. Consequently the impression has been formed that the meningiomas are better risks preoperatively. However, in the past 5 years, it has been customary to observe carefully the serum protein level in these patients. If the level is low preoperatively or postoperatively, immediate efforts are made by prompt use of amigen or blood to restore it to normal (5). Whole blood is used routinely at present in what, 10 years ago, would have been considered enormous amounts to maintain hemoglobin and blood pressure levels. In 27 of the last 93 operative sessions, the patients received 1000 cubic centimeters, or more, of whole blood, plus at least 500 cubic centimeters of normal saline; and in 7, 1500 to 2000 cubic centimeters were administered during, or within 12 hours after, the craniotomy. The recent suggestion (6) of prebleeding and subsequent autotransfusion has not been attempted. All our tumor cases are given 2500 to 3000 cubic centimeters of intravenous fluid in the first 24 hours postoperatively. I am not entirely convinced that all the blood given is essential. But, with the establishment of a bank in the hospital, blood is always available and these patients, unquestionably, are in better condition at the end of 48 hours postoperatively than they were 5 or 10 years ago, when less blood was used. Shock from exsanguination following removal of a meningioma is no longer seen.

All cranial tumor surgery in this clinic is carried out with patient in the horizontal position. The erect, or sitting, position is used only in trigeminal root sections. Local anesthesia, plus morphine, is the anesthesia of choice in craniotomy for a supratentorial tumor. An adult who is not stuporous preoperatively receives ¼ grain of morphine an hour before coming to the theater. Restlessness during operation is controlled by $^{1}/_{12}$ grain of morphine or by small amounts of sodium pentothal injected into the intravenous tube. In all suboccipital craniectomies, with patient in the prone position, endotracheal ether is used. The importance of the free air-way afforded by the endotracheal tube cannot be overemphasized. Venous congestion, with consequent increase in intracranial pressure which even a tap of the ventricle will not relieve, is avoided. I know of no more dreadful situation that the neurosurgeon can face than to have the posterior fossa open, have something go wrong with the anesthesia, with consequent coughing and straining by the patient, which may in a short 30 seconds so congest his cerebellar hemispheres that they bulge out of the wound. Any further attempt

at tumor extirpation is impossible and, unless something can be done by deepening the anesthesia or repositioning the patient's head, the operator may at times have trouble in closing the muscles. All this has been avoided, in our experience, by skillfully administered endotracheal ether. That, following the introduction of an endotracheal tube, the patient has an increase in his laryngeal secretion, from irritation of the tube, seems certain. And increase of laryngeal secretion may lead to aspiration pneumonia, especially since damage to the vagus and glossopharyngeal nerves with vocal cord paralysis and loss of cough reflex not infrequently accompany removal of a meningioma from the posterior fossa. But the advantages of a clear air-way and consequent absence of pressure during tumor extirpation far outweigh this disadvantage.

Careful hemostasis during the approach to a meningioma is, of course, essential. Scalp, pericranium, bone, and dura, all, may be highly vascular. Preoperative ventricular tap for relief of pressure will help reduce bleeding. Electrically driven drills and saws save time in turning down flaps. Speed in elevating the bone flap, separating it from the tumor, if the lesion has penetrated the dura, or exposing the dura and promptly coagulating its many bleeding points, saves unnecessary loss of blood. Motor driven tools have halved the time required to turn down a flap. Once the tumor is exposed and its dural attachment cut off from adjacent vessels and thoroughly coagulated, the most severe, early hemorrhage is controlled. In tumors attached to the dura overlying the convexity of the brain, the problem is relatively simple. Is the patient's condition sufficiently satisfactory to withstand the removal of a tumor presumably of some size? Once the cortical vascular connections to the tumor have been secured, a simple matter with electrocoagulation, but little bleeding usually occurs from deeper vessels. In 5 of our patients, disaster followed what seemed to be the relatively bloodless removal of a convexity tumor. In every instance, the tumor was large, weighing between 150 and 200 grams. Cortical resection was necessary in each case to obtain sufficient room to deliver the tumor. In 3 cases, the blood pressure dropped out suddenly about 30 minutes after the tumor had been removed, after hemostasis was apparently complete, and the wound ready for closure. In the other 2 cases, shock appeared an hour after return to the ward. In all these instances, no amount of intravenous fluid or pressor substances were of any avail. In no case did autopsy show hemorrhage of any amount into the tumor bed. These tumors were all of sufficient size to have compressed the midbrain. Possibly a too sudden removal of the tumor with too abrupt release of midbrain pressure caused failure of sympathetic control.

When a meningioma lies along the midline, the ease or difficulty of its removal depends upon the extent of its attachment to the falx, whether or not the longitudinal sinus is invaded and the rolandic vein compromised. If the dura between the longitudinal sinus and the tumor can be transsected, much of the blood supply to the tumor is cut off. In these tumors attached to the sinus, the better method of attack is to deliver them from the brain laterally and swing them medially across the sinus. Then the extent of sinus involvement can be seen from the undersurface of the dura, and a better chance is had to shave the dura off close to the sinus without entering it. Incomplete removal of a tumor in this position is often unavoidable, particularly if the sinus is involved behind the entrance of the rolandic vein. Injury to the sinus in this region, unless it has been invaded and obstructed by the tumor, will lead to disastrous neurologic sequelae. Coagulation of any tumor remnants lying against the falx close to the sinus is, of course, indicated. If the sinus has been invaded and obstructed by tumor, its excision, plus the adjacent dural attachment of the tumor, should be carried out. Recently, in a large, bilateral, frontal tumor in this series, the anterior 15 centimeters of falx, with both superior and inferior longitudinal sinuses, were removed with the tumor. Fortunately, no motor symptoms developed, since the venous return had already been obstructed.

In the removal of sphenoid ridge or olfactory groove meningiomas, the hazard is damage to the carotid artery or its branches. In right-handed persons, amputation of the right

frontal lobe is always justified if, thereby, a better exposure can be obtained. The carotid vessels are always behind and below the tumor. The right anterior cerebral can usually be clipped without causing neurologic sequelae. Complete removal, with dural attachment, of a large meningioma in this subfrontal area requires skill, courage, and a certain amount of luck. A very close calculation must be made. Should the inner third of the tumor be completely removed, when enough has already been extirpated to produce great relief of symptoms, while further attempt may tear the carotid, with hemiparesis certain to follow its ligation?

The results of surgical attack upon a meningioma in the posterior fossa depend upon the relationship of the tumor to the vagus nerve and brain stem. Many of these tumors spring from the arachnoid fibroblasts in the porus acusticus internus and are no more difficult or dangerous to remove than an angle tumor. The vagus lies loosely along the lower pole of the tumor and can be readily separated from it. A second group arises from the edge of the posterior lacerated foramen and involve the vagus directly. Removal of such a tumor is impossible without total injury to the vagus and glossopharyngeal. If these nerves are injured, with ipsolateral vocal cord paralysis and loss of the gag reflex, great care is necessary to prevent aspiration pneumonia postoperatively. Tracheotomy is often necessary, and feeding by stomach tube essential for long periods, to prevent disastrous pulmonary complications.

After the removal of a cerebral meningioma, should the dural defect produced by excision of the attachment of the tumor to this membrane be repaired by a fascia lata or temporal fascia graft? If the defect lies over the motor cortex, we like to sew in a graft, on the theory that irritative convulsive attacks are less likely to occur postoperatively. In other cases, a graft may or may not be introduced. In this series, in 44 instances, a large dural defect remained after removal of the tumor. The excised dura was replaced by a graft in 26 instances. One of these, a patient in whom a fascia lata graft was used, died of meningitis. But if the flap is wired and the galea and skin are carefully closed, it seems to make little or no difference whether or not the dura is repaired. In the last years, fewer bone flaps have been completely sacrificed. In 84 cases, complete sacrifice of the flap seemed indicated in 18. Whenever possible, that part of the bone grossly involved by the tumor is reamed out with the electric burr and the remainder of the flap replaced (see Fig. 6, b). Our records show 7 cases in which this was done over 5 years ago, and no evidence of recurrence is apparent. The patient is often spared an unsightly cranial defect if part of the bone flap can be replaced. In 3 instances, the flap was removed, boiled at once for 3 minutes, and reinserted. One of these reinserted flaps was lost 2 months later from infection.

RESULTS

In this group of 149 meningiomas, there were 25 operative and 3 nonoperative deaths, a total of 28 in all. Of the 121 survivors, we have, through the efforts of the tumor registry, been able to check accurately on 113. Eleven are known to have died since 1935 either from a recurrence of the tumor, in 7 cases, or from intercurrent disease, in 4 instances. Among the 102 survivors, 34 are known to be alive and well and working at their previous or similar jobs, in as good physical condition as they were prior to the removal of the tumor. The breakdown of the figures in this group is given in Table I. It will be noted that in 31 of these 34 cases, the tumor was completely removed, so that this group can be considered to have been cured and restored to their previous economic condition. In 3 instances, the tumor was partially removed and, therefore, it may be presumed that a recurrence with return of symptoms can be expected.

In this group of 149 meningiomas, therefore, 31, or 20 per cent, can be considered to have been completely relieved of all their symptoms following total operative removal of the tumor. Sixty-eight other cases survived but are handicapped by postoperative complications. Seventeen are incapacitated by loss of vision, present in each instance prior to operation to a greater or less extent. In 4 of those cases, high choked disc was recorded

preoperatively, although visual acuity was adequate. Following the removal of the tumor, in spite of the relief of the pressure, there was a continuation of the visual loss. In 31 cases, the postoperative complication is convulsive attacks. In 21 of these cases, convulsions were present preoperatively and postoperatively; in 10, they developed as a result of the operative procedure. Fifteen of these are men, 16 are women. The women can carry on their occupations as housewives, etc. in a fairly satisfactory manner, but the men have always been compelled to change their job, owing to their convulsive attacks. In 15 of these cases, the convulsions are well controlled by phenobarbital and occur only every 4 to 6 months. In the other 11 cases, the fits are more frequent, coming on, on the average, every 2 weeks.

The 20 remaining patients, 13 women and 7 men, are handicapped either because of a complete or partial hemiparesis or spasticity in the contralateral extremities. Here again, 13 are able to live reasonably useful lives, but 7 seem to be badly incapacitated.

Considering the whole group of 149 patients, 163 operations were performed with 25 deaths. As has been stated, 7 patients were operated upon in two stages, 4 patients were operated upon twice, and 3 patients, three times, for recurrence. The overall mortality is 15.5 per cent.

From January 1, 1936, to December 31, 1940, 79 operations were performed on 71 patients, with 17 deaths, a case mortality of 24 per cent and an operative mortality of 21 per cent. From January 1, 1941, to December 31, 1946, 84 operations were performed on 75 patients, with 8 deaths, a case mortality of 10.6 per cent and an operative mortality of 9.5 per cent. To April 1, 1947, 7 additional meningiomas have been removed without a fatality. In the last 82 cases, 93 operations have been carried out with 8 deaths, a case mortality of 9.7 per cent and an operative mortality of 8.6 per cent.

CONCLUSION

A review of 10 years' experience with 149 cases of intracranial meningioma, indicates that, by proper methods, diagnosis and localization of the tumor can be correctly made in 98 per cent of the cases. Electrosurgical aids, suction, and especially preoperative and postoperative supportive measures, plus prompt and adequate control of intracranial pressure, have reduced the operative mortality in recent years from 21 to 8.6 per cent. These tumors are benign. Complete removal, with dural attachment, precludes recurrence. The surgeon should always keep this fact in mind. His problem is total extirpation of the tumor with minimum damage to adjacent brain areas, thus reducing neurologic sequelae. In spite of electrosurgery, suction, ventriculography, blood transfusions, the record here presented might well have been improved if a more conservative attack, as represented by a two stage procedure, had been employed with greater frequency. The temptation to indulge in "brilliant" surgery, and the prompt, one stage enucleation of a meningioma seems, at times, to be overwhelming. But if the "score," as represented by a lowered mortality rate is to be improved, this impulse must be sternly suppressed.

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THE RH FACTOR IN OBSTETRICS

Report of 572 Cases of Infants of Rh Negative Mothers, 232 of Whom Received Transfusions of Mother's Blood

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WITH the growth of our knowledge of the Rh factor have come tentative applications in the field of obstetrics. It is supposed, for instance, that hemolytic disease of the newborn, or erythroblastosis, has its origin in a difference of the Rh factor in mother and infant. It is thought that the red cells in the fetal blood, passing through the placenta and entering the mother's blood stream, set up an anti-Rh agglutinin which in turn passes back to the fetal blood. Given sufficient agglutinins, some form of blood dyscrasia results, before, at, or soon after birth, with a high mortality in the case of erythroblastosis. This theory of the causation of hemolytic disease of the newborn has not yet been proved, but a greater incidence of erythroblastosis in infants of Rh negative mothers than in infants of Rh positive mothers has been proved statistically. Hence it has become usual to expect erythroblastosis when an Rh negative mother has a history of loss of infants. Two prophylactic measures have been advocated: cesarean section at 8 months, and cord transfusion at birth. If and when the disease becomes manifest, transfusions are the treatment of choice.

Since difference in the Rh factor in the mother's blood is assumed to be the cause of the disease, great stress has been laid on giving the child, not the blood of its mother, but that of an Rh negative group O donor. The contention of this paper is that blood of the mother can and should be given, and two series of cases are presented of infants of Rh negative mothers delivered in a 3 year period at the Methodist Hospital in Brooklyn. In the first, mother's blood was given prophylactically at birth; in the second, no prophylactic transfusion was given and when transfusions were indicated, donor's blood was given. In the first group, of 231 infants living at birth, there were 9 deaths, 7 in prematures, 2 in full term. There were no deaths from erythroblastosis. In the second group, of 322 infants living at birth, there were 9 deaths, 2 in prematures, and 7 full term, 5 of erythroblastosis, 4 of other causes. Of the 5 infants who died of erythroblastosis, 4 received transfusions, 1 none. No untoward effects from the transfusions with mother's blood were noted, and in a few cases in which additional transfusions were needed and donor's blood was used, reactions were practically nonexistent, in contrast to the cases in which donor's blood was used exclusively.

A brief discussion is included of 10 cases of erythroblastosis that occurred earlier than the 3 year period reported; in 9 the father's blood was used, in 1, both the mother's and father's blood.

Six cases of possible blood dyscrasia in infants of Rh positive mothers, occurring during the period studied, are also briefly discussed.

BLOOD STUDY

We have been criticized for giving the blood of Rh negative mothers, to their babies, but our excellent results have encouraged us to continue. We have had cases of severe reaction following the use of Rh negative donor's blood, group O, supposedly compatible, and not infrequently transfusions of donor's blood causes little or no change in the blood picture. In marked contrast, with the use of mother's blood no reactions occur and the blood picture improves promptly. In order to justify our use of Rh negative mothers' blood, we made the following blood studies.

In 100 of the babies of Rh negative mothers who received prophylactic cord transfusions of

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mother's blood at birth, the number of red cells was averaged after the cord transfusion and found to be 6,465,000. The largest number was 9,100,000, and 3 babies had 8,000,000. The lowest count was 3,600,000, and in this baby the hemoglobin was 100 per cent. In 2 of the babies hemoglobin was 170 per cent, and in one 168 per cent. The large number of red cells and the high percentage of hemoglobin did not seem to trouble the babies, and the return of the blood count to normal did not cause jaundice.

In 100 babies of Rh negative mothers who did not receive prophylactic cord transfusions, the average number of red cells was 5,787,000, or 678,000 less than in those who received cord transfusions.

One indication of compatibility between bloods is increase in red cells following a transfusion. If the blood of Rh negative mothers is incompatible, one would expect a decrease in red cells following a transfusion, but in no instance was this evidence of incompatibility, or any other evidence noted.

In 80 Rh negative mothers whose blood was matched and cross-matched with blood of their babies, some agglutination was found in 23 cases. When the mother's cells were matched with the baby's serum in these 23 cases there were only 10 cases in which there was any agglutination, and 3 of these were slight. Two of the 10 were rechecked and no agglutination was found. Difference in type rather than the Rh factor seemed to cause agglutination.

Twelve babies of the 80 Rh negative mothers whose blood was thus studied received a prophylactic cord transfusion. In 1 case, infant's and mother's blood were not compatible by either the slide or water bath method. The baby received 25 cubic centimeters of its mother's blood. Following the cord transfusion red cells were 4,800,000, hemoglobin 138 per cent; on the second day hemoglobin was 144 per cent. The baby made an uneventful recovery.

In 46 Rh positive mothers whose blood was matched and cross-matched with blood of their babies, agglutination occurred in 6, and in 1 of these 6 the mother's cells were incompatible with baby's serum.

TABLE I.—RH FACTOR

Determinations				Deliveries	Rh negative deliveries		
Year	Positive	Negative	Total		Received mother's blood	Did not receive mother's blood	Total
1944	1,616	294	1,910	2,066	77	59	136
1945	2,089	383	2,472	2,086	96	92	188
1946	2,285	365	2,650	2,337	59	189	248
	5,990	1,042	7,032	6,489	232	340	572

TRANSFUSION STUDY

In an approximately 3 year period, spring 1944 through 1946, at the Methodist Hospital in Brooklyn, the Rh factor was determined in 7,032 women, and 1,042, or 14.7 per cent, were Rh negative. This percentage agrees with other findings on the incidence of Rh negative individuals in the general population (Table I).

Of the 1,042 Rh negative women, 572 were delivered in the 3 year period. About 40 per cent, 232 babies, received transfusions of mother's blood; the remainder, 340, had either no transfusions or transfusions of Rh negative compatible donor's blood. All transfusions of mother's blood were prophylactic, by cord at birth, except 3, which were given in the presence of erythroblastosis within a few hours or days after birth. In the other group there were 3 prophylactic transfusions of donor's blood. These transfusions have been included in the groups according to the blood used (Table I).

In the group of 232 infants who received mother's blood, 229 by cord transfusion at birth, there were 9 deaths, 7 in prematures and 2 in full term infants, one of epidemic diarrhea, the other from an intestinal obstruction due to a congenital defect. There were 35 prematures, and 13 infants who showed some evidence of blood dyscrasia. Nine cesarean sections were done in the group with 1 death, a premature, gestation 34 weeks. Two other prematures were delivered by section. Conditions at birth were: good, 207; fair, 17; critical, 8; stillbirth, 1. There were 56 primiparas, 176 multiparas (Table II).

In the group of 340 not given prophylactic transfusions of mother's blood, there were also 9 deaths, 2 in prematures, 7 in full term, 5 of erythroblastosis, and 4 of other causes. There

TABLE IIA.—RH FACTOR

Year	Rh delivered	Mother's blood cord transfusions					Donor's blood or no transfusions				
		Total	Erythroblastosis		Prematures		Total	Erythroblastosis		Prematures	
			Number	Died	Number	Died		No.	Died	No.	Died
1944	136	77	2	0	11	2	59	2	2	—	—
1945	188	96	5	0	13	1	92	8	1	5	1
1946	248	59	6	0	11	4	189	8	2	7	1
	572	232	13	0	35	7	340	18	5	12	2

were only 12 prematures in the group, since most of the prematures received cord transfusions. There were 18 cases of erythroblastosis, with 5 deaths, 4 transfused with donor's blood, 1 not transfused. Fourteen cesarean sections were done in the group with loss of 2 infants, one a stillbirth, the other from erythroblastosis. Another case of erythroblastosis with recovery occurred in an infant delivered by cesarean section. Conditions at birth were: good, 305; fair, 15; critical, 2; stillbirth, 18. There were 151 primiparas, 189 multiparas (Table II).

ERYTHROBLASTOSIS IN INFANTS GIVEN RH NEGATIVE MOTHER'S BLOOD

Of the 232 infants of Rh negative mothers who received transfusions of mother's blood, 13, or 6 per cent, either showed evidence of blood dyscrasia or there was a history of it (Table III). Two of the babies had more than 50 normoblasts to the 100 white cells, and 6 had more than 15. Blood counts showed that 8 had 4,500,000 or less red cells and 5 of these were under 4,000,000. It is interesting to guess what the blood count would have been had these babies not been transfused. The hemoglobin was 110 per cent or under in 9 of the babies, and in 5 it was under 100 per cent. Eight of the babies were jaundiced, and in 5 the jaundice was very marked.

The 13 mothers had a total of only 20 living children out of 31 pregnancies, and every one of the 13 was a multipara. Five had had 1 previous pregnancy; three, 2; three, 3; one, 4 with no living children; one, 7.

Of the 10 babies who received a cord transfusion, 4 received additional transfusions of

TABLE IIB.—PARITY OF RH NEGATIVE MOTHERS

Year	Mother's blood cord transfusion			Donor's blood or no transfusion		
	Primip.	Multip.	Total	Primip.	Multip.	Total
1944	35	42	77	27	32	59
1945	13	83	96	34	58	92
1946	8	51	59	90	99	189
	56	176	232	151	189	340

Rh negative donor's blood; 2 had 1; 2 had 2 additional transfusions. It was noticed that there were no reactions to these transfusions of donor's blood. In the presence of erythroblastosis 3 infants not given transfusions at birth were given large transfusions of mother's blood, 75 to 90 cubic centimeters intravenously, several hours or days after birth, and all 3 received additional transfusions of donor's blood. There were no reactions to the mother's blood, even in 1 case in which the mother's blood had a high titer of anti-Rh agglutinins (Case 3 following; previously reported in 1946, 6). In 1946, the last year of the period studied, no additional transfusions were needed in babies receiving prophylactic transfusions of mother's blood.

All of the babies were discharged on or before the 14th day. The smallest weighed 5 pounds 5 ounces, and was of 36 weeks' gestation. Judging from the birth weights of these 13 babies, premature induction of labor when erythroblastosis is anticipated is not justified.

From the results it seems fair to conclude that cord transfusion prevents onset of the disease, and if it develops, hastens recovery. Since the disease can be anticipated more readily in multiparas, our tendency was to give prophylactic transfusions to infants of multiparas rather than of primiparas; in 1945 and 1946, 134 infants of multiparas were transfused as compared to 21 of primiparas (Table IIB).

Of the following cases, the first 2 illustrate very probable aborted erythroblastosis: in the first, the mother had a bad history and blood studies indicated prognosis of the disease; in the second, the baby was active and in good shape in spite of some evidence of the disease. In the third and fourth cases the babies were not given prophylactic transfusions, but when

TABLE III.—ERYTHROBLASTOSIS, 13 BABIES TRANSFUSED WITH MOTHER'S BLOOD

Year	Hospital No.	Age of mother	Gravida	Living children	Normos.		R.B.C. million	Hb. %	Cord transfusion	Intravenous	Jaundice	Day of discharge	Birth weight	
					Cord	1st or 2nd day								
1944	26739A	25	ii	1		29	3.8	94		85M 100Rh–		12	6–14	Baby made an excellent recovery
1944	29960	31	iii	1		25	2.9	78	40	125Rh– 90Rh–	xxxx	11	7–3	Marked poikilocytosis. Anemia of the newborn
1945	31623	27	iv	3		17	4.2	115	35	110Rh– 55Rh–	xxxx	14	8–2	Moderate anisocytosis.
1945	24865A	34	iii	2		22	4.5	95		80M 90Rh–	xx	11	6–14	Baby gained steadily after each transfusion
1945	30557	29	ii	1		13	5.6	110		90M 90Rh–	xxxx	14	10–0	Mother had a high titer of anti-Rh agglutinins.
1945	25763A	25	ii	1		5	3.0	82	40	125Rh–	xxxx	10	9–2	Marked jaundice. Spleen 1½ fingers below costal margin.
1945	13725B	35	iii	2		12	3.8	100	20	160Rh–	x	12	7–7	Spleen 2 fingers below costal margin.
1946	30481	26	ii	1		18	6.1	108	40		xxxx	12	6–9	Baby very active in spite of severe jaundice.
1946	32068	25	ii	1	53	30	7.3	144	45			12	5–5	Baby premature 36 weeks.
1946	11271G	39	viii	4	93	77	4.4	108	50			12	10–8	Mother had lost 3 children, 2 of which were stillbirths.
1946	23279D	32	v	0			3.8	95	50		xx	11	6–3	Mother had lost 5 children, 2 a set of twins.
1946	26537B	30	iv	1		6	6.5	124	40			11	7–10	An only living child had had a cord transfusion.
1946	29685A	29	iv	2	20		5.5	120	35			10	8–4	Baby had minor convulsions for 6 days. Normal at 6 weeks.

the disease developed the mother's blood was given, with excellent results, in 1 case in spite of a high titer of anti-Rh agglutinins.

CASE REPORTS (GROUP A)

CASE 1. Baby G. 23279G. This mother was a quintigravida, Rh negative, with no living children, and had been married 6 years. Her first pregnancy ended in a 4 months' miscarriage. In 1942 she had premature twins; both died. In 1944 she was delivered of an 8½ months' baby which was not transfused and which died from erythroblastosis on the third day. In 1945 she had a 4 months' miscarriage.

Her last child was born May 26, 1946. The patient was now 32, had been pregnant 5 times, and had no living children. She came to me shortly after becoming pregnant and was given 20 minims of wheat germ oil daily, ¼ grain of protiodide of mercury twice daily, and until the pregnancy had reached 5 months, 3 cubic centimeters of corpus luteum extract weekly by injection. The delivery was an easy Barton rotation of a right occipitoposterior position and low forceps. The baby was immediately given 50 cubic centimeters of its mother's blood by cord transfusion; there was no reaction. The baby was of 39 weeks' gestation, cried spontaneously, had a good color and weighed 6 pounds 3¾ ounces. The mother was Rh negative, the father Rh positive and the baby Rh positive. The placental blood showed 3,800,000 red cells and the hemoglobin was 95 per cent. Following the transfusion the red cells were 4,050,000 and the hemoglobin 150 per cent. There were no normoblasts.

On the day following delivery the baby was slightly jaundiced and this increased considerably. There were also areas of ecchymoses over the body most noticeable on the extremities. In spite of the jaundice and the ecchymoses the baby seemed to be doing nicely and the red cells and the hemoglobin increased. On the second day following delivery, the red cells were 5,700,000 and on the fourth, 6,600,000 with a hemoglobin of 147 per cent. When the baby was 8 days old the hemoglobin was 136 per cent and the red cells 5,980,000. The baby was somewhat dehydrated on the fifth day and was given 50 cubic centimeters of saline solution by clysis. The baby was breast fed, and was discharged from the hospital on the eleventh day weighing 5 pounds 14 ounces. At the end of 6 weeks it was still breast fed and was doing nicely.

In anticipation of erythroblastosis I had had complete blood studies made in this case. The mother's blood was examined by Dr. Levine on four occasions before delivery and found to be Rh negative, group O. Her husband was also group O but Rh positive and also Hr positive. This Dr. Levine thought confirmed the prognosis of incompatibility of the in-

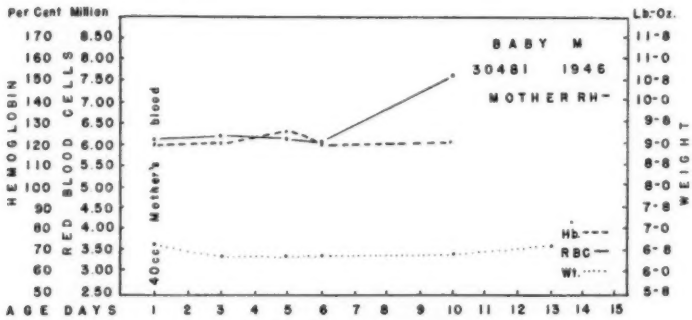

Fig. 1. Erythroblastosis fetalis. Case 2.

fant's blood. Three days before delivery Mrs. G.'s blood contained weak but distinct blocking antibodies, and Dr. Levine thought there was a good possibility of an infant affected with erythroblastosis, but not too severely affected.

It is very hard to make a definite diagnosis of erythroblastosis in this baby. I am certain, however, it would have died from the disease had it not received a transfusion of Rh negative blood. Had the transfusion been delayed until definite symptoms of erythroblastosis developed, one transfusion would not have been enough to save the child, and if Rh negative blood from some other donor than its mother had been used there might have been incompatibility. Mother's blood is apparently always compatible, and if there are anti-Rh agglutinins they do not seem to trouble the baby.

CASE 2. Baby M., 30481 (Fig. 1). The mother of this baby was a secundigravida, primipara, 26 years old. The mother was Rh negative and the father Rh positive. She had had a normal baby in 1944. Her second child was delivered March 6, 1946, and was given 40 cubic centimeters of mother's blood by cord transfusion as a prophylactic procedure. The condition of the baby was good at birth. It weighed 6 pounds 9½ ounces; blood count showed 6,150,000 red cells, hemoglobin 123 per cent with 18 nucleated red cells. The following day the baby was extremely jaundiced but very active and otherwise seemed normal. It was breast fed. The red cells remained slightly over 6,000,000 until the eighth day, when they were 7,530,000, with 10 nucleated red cells. The baby was discharged on the 12th day having gained back its birth weight. If the jaundice in this case had been due to blood destruction, there should have been a decrease in the hemoglobin and red cell count. The jaundice must have been due to blocking of the bile ducts or damage to the liver from disease.

CASE 3. Baby A., 30557. This case has been previously reported in 1946 (6). The mother was thought to be Rh positive. No cord transfusion was given at birth. The baby soon became very jaundiced and seemed to be in critical condition supposedly due to an obstruction of the bile ducts. The baby was given 90 cubic centimeters of its mother's blood, and on the following day it looked like a normal baby except for its color. The blood count was normal until the eighth day, when the red cells were 4,200,000 and the hemoglobin was 80 per cent. When the baby was 14 days old the red cells had dropped to 2,700,000 and the hemoglobin was 60 per cent. The baby was then transfused with 90 cubic centimeters of Rh negative blood from a compatible donor.

When the mother's blood was tested by Dr. Levine several days after the child's birth, it was found to be Rh negative with the high titer of 1:80. This baby was undoubtedly suffering from erythroblastosis and was cured by the use of the mother's blood which contained a high titer of anti-Rh agglutinins.

CASE 4. Baby F., 24865. Mrs. F. was a tertigravida, secundipara, 34 years old, and Rh negative. She had had a normal baby in 1938, and in 1941 had toxemia of pregnancy, was delivered at 8 months of a baby weighing only 3 pounds 10 ounces. On April 4, 1945 she was delivered of a male child weighing 6 pounds 14 ounces. The mother was thought to be Rh positive and no cord transfusion was given. Soon after birth the baby became very jaundiced; the hemoglobin was 96 per cent, red cells 3,520,000, and there were 29 normoblasts per 100 white cells. The baby was given 80 cubic centimeters of its mother's blood. There was no reaction, and the baby did well until it was 10 days old, when the hemoglobin was 70 per cent, red cells 3,400,000. At this time a transfusion of 90 cubic centimeters of blood from an Rh negative donor was given, and the baby was discharged on the eleventh day weighing 8 ounces above its birth weight.

ERYTHROBLASTOSIS IN INFANTS NOT GIVEN RH NEGATIVE MOTHER'S BLOOD

There were 18 cases of erythroblastosis among the 340 infants not given transfusions of mother's blood. One died without receiving any transfusion and would probably have lived had it received a prophylactic transfusion of compatible blood (Case 10). In the re-

TABLE IV.—ERYTHROBLASTOSIS, 17 BABIES TRANSFUSED WITH DONOR'S BLOOD

Year	Hospital No.	Age	Gravida	Living children	Normos.	R.B.C. 1st day	R.B.C. low	Hb. % 1st day	Hb. % low	Number trans.	Amt. blood	Day of discharge	Jaundice	
1944	25184	28	ii	1	142	4.9	4.9	108	108	1	105	2	x	Died. Transfusion no effect on normoblasts.
1944	24786B	28	ii	1	No	4.8		112		1	25	4	xxxx	Died. Autopsy. Hematopoiesis in liver.
1945	31645	33	ii	1	3	5.6	4.8	137	115	2	150	14	x	Section. Difficulty in resuscitation.
1945	19343C	36	iv	1	375	3.8	2.8	60	46	2	145	11	x	1st baby had 510 normos.
1945	30423	35	ii	1	10	4.1	2.6	96	54	7	460	36	xxxx	Transfusion had little effect on weight or hemoglobin.
1945	31807	24	ii	1	No	3.8	3.2	86	61	6	505	24	xx	Rh– blood apparently not compatible
1945	31198	25	ii	1	33	6.8	4.9	160	150	2	170	12	x	Mother transfused following first delivery.
1945	30558	34	iv	1	2	5.2	5.2	139	135	1	50	12		No evidence of erythroblastosis. Cord trans. Rh– blood.
1945	31723	25	i	0	12	5.7	5.6	138	132	1	40	12	x	Premature, 4 lb. 5 oz. Cord transfusion.
1946	32090	28	ii	0	12	6.8	6.2	139	130	1	40	12		Mother previous transfusion reaction. Baby had cord transfusion.
1946	27141	24	iv	1	94	5.7	4.5	124	92	2	150	13	x	Large spleen. Normoblasts increased from 15 to 94 after trans.
1946	26237A	30	ii	1	64	4.1	3.8	111	92	2	165	17	xx	Baby normal at birth. Normos. increased from 10 to 64 fol. tr
1946	32578	33	iii	2	110	2.1		43		1	85	1		Died. Marked reaction to trans. Died 9 hours later.
1946	30133A	22	ii	2	1	2.8	2.8	95	93	1	20	2	xxxx	Transfusion too small. Spleen enlarged. Died.
1946	32808	25	ii	1	0	5.0	4.7	140	98	1	75	11		Marked drop in hemoglobin by 3rd day. No other evidence of erythroblas.
1946	32946	24	i	0	0	5.8		135	65	2	105	17	x	Hemoglobin 65% on 2nd day. Rapid recovery.
1946	19266A	36	v	4	8	3.5	3.3	94	45	4	355	21		Liver and spleen palpable. Mother's and baby's bloods compatible.

maining 17 cases there were 4 deaths (Table IV).

Five of the babies had more than 50 normoblasts and 1 between 15 and 50, a total of 6 with more than 15 normoblasts. Red cells were less than 4,500,000 in 7 and less than 4,000,000 in 5. Twelve were jaundiced, 3 markedly.

The 17 mothers had a total of 19 living children out of 25 pregnancies. Two were primiparas. Of the 15 multiparas, 10 had 1 previous pregnancy; one, 2; three, 3; one, 4.

A total of 37 transfusions was given the 17 babies, in contrast to the ratio of 22 to 13 in the mother's blood group. Eight received only 1 transfusion; 6 needed 2; one, 4; one, 6; and one, 7. One received a total of 460 cubic centimeters, one 505. Five remained in the hospital longer than 14 days, 1 for 36 days.

Four of the babies died. One, with 142 normoblasts received a single transfusion of 105 cubic centimeters of Rh negative blood. The transfusion had no effect on the normoblasts, and the baby died on the second day. This was one of two in the group born by cesarean section. Two died following very small transfusions, probably too small. One had a severe reaction following the first 15 cubic centimeters of Rh negative blood; the transfusion was continued and a total of 85 cubic centimeters given; the baby died 9 hours following delivery.

It is interesting to observe that of the 4 who lived after receiving only 1 transfusion, 3 received a cord transfusion at birth.

The cases which follow show how many transfusions are necessary to cure the disease once it has appeared. The last case illustrates

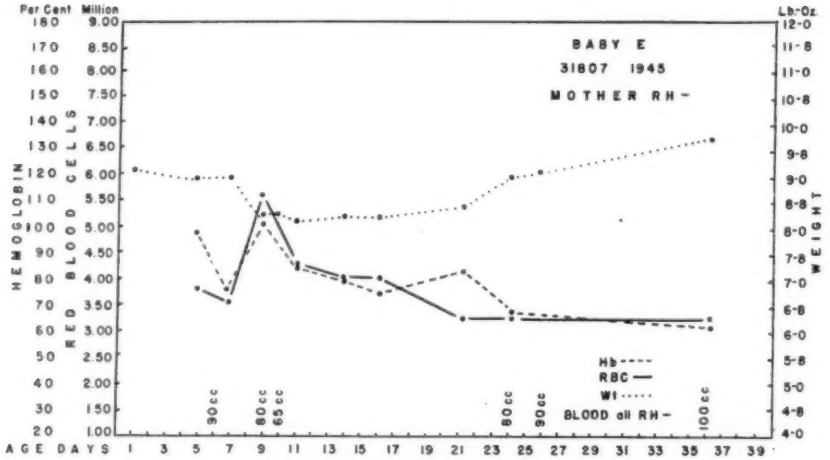

Fig. 2. Erythroblastosis fetalis. Case 5.

the successful use of a prophylactic cord transfusion with donor's blood in the presence of possible erythroblastosis.

CASE REPORTS (GROUP B)

CASE 5. Baby E., 31807, (Fig. 2). The mother of Baby E. was 24 years old, secundigravida, Rh negative. She had 1 normal child, born in 1944. On December 25, 1945 she was delivered of a baby girl weighing 9 pounds 2 ounces. The child seemed perfectly normal at birth, but 4 days later it was moderately jaundiced; the spleen was not palpable. The blood count showed 3,840,000 red cells and a hemoglobin of 98 per cent. There were no nucleated red cells. When the baby was 6 days old the red cells were 3,500,000 and the hemoglobin 76 per cent. The baby was given 90 cubic centimeters of Rh negative blood from a supposedly compatible donor. On the ninth day the baby was transfused with 80 cubic centimeters of Rh negative blood, and with 65 cubic centimeters on the tenth, but in spite of the 3 transfusions there was no increase in either the red cell count or the hemoglobin. The baby received 3 more transfusions and was discharged from the hospital on the 24th day. This baby received 6 transfusions for a total of 505 cubic centimeters of blood. In spite of the repeated transfusions the baby improved very little. On January 29, when the baby was 34 days old, the red cells were 3,330,000 and hemoglobin 63 per cent.

CASE 6. Baby O., 30423A, (Fig. 3). The history of this baby and the results are very similar to those of the preceding case. The mother was 35 years old, secundigravida, unipara, Rh negative. She had had 1 normal pregnancy. On January 6, 1946 she was delivered of a full term female infant weighing 8 pounds 2 ounces. The blood count on the day following delivery was 4,150,000 and the hemoglobin 100 per cent with 10 normoblasts. The spleen was enlarged, and erythroblastosis was suspected. The baby was given 60 cubic centimeters of Rh negative blood. Following the transfusion the baby became very cyanotic and stopped breathing. Respirations were re-established with some difficulty. The baby received a 40 cubic centimeter transfusion on the 5th day and 85 cubic centimeters on the 7th. The 3 transfusions had little effect on the blood count, and by the time the baby was 11 days old, the red cells were 2,700,000 and the hemoglobin 60 per cent. When the baby was 25 days old the red cells were 2,860,000 and the hemoglobin 60 per cent. The baby was discharged on the 36th day. The baby had a total of 7 transfusions and 460 cubic centimeters of Rh negative blood.

There is little doubt but that the Rh negative blood used for these two babies was not compatible. If the blood had been compatible the severe reaction would not have occurred in the second case, and the repeated transfusions in both cases would have been unnecessary.

CASE 7. Baby B., 27141. This child's mother was a quartigravida, unipara, 24 years old and Rh negative. She had had 1 normal baby and 2 miscarriages. A normal baby was born on March 23, 1946, weighing 6 pounds 15 ounces. At birth the blood count showed 5,720,000 red cells and 111 per cent hemoglobin, with 3 normoblasts. When the baby was 6 days old the spleen was enlarged, the hemoglobin was 98 per cent and there were 15 normoblasts. It was given 75 cubic centimeters of Rh negative blood. Four days following the transfusion the normoblasts were 37 per 100 white cells. When the baby was 13 days old the normoblasts had increased to 94. The hemoglobin was 92 per cent and the red cells 4,590,000. The baby was given another transfusion of 75

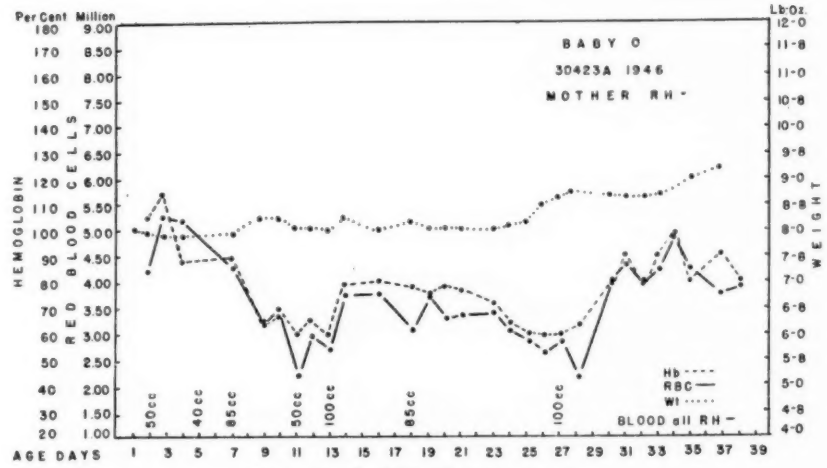

Fig. 3. Erythroblastosis fetalis. Case 6.

cubic centimeters of Rh negative blood. It is interesting that the normoblasts should increase following the use of Rh negative blood. It apparently indicates an incompatibility.

CASE 8. Baby D., 19266A. This mother was 36 years old, quintigravida, quartipara, group B, Rh negative, and her husband was Rh positive. The mother had had 4 normal deliveries, but following the last, in 1944, she had 2 transfusions. Her fifth child was born October 4, 1946, a male child weighing 7 pounds 11 ounces. The baby's condition was good at birth. A cord transfusion of mother's blood was attempted and failed. The baby was found to be Rh positive. On the day following delivery the red cell count was 3,500,000 and the hemoglobin 94 per cent. On October 6, the hemoglobin was 45 per cent. The baby was jaundiced, liver and spleen enlarged, and 35 cubic centimeters of Rh negative blood were given. On October 7, the red cells were 3,300,000 and the hemoglobin 93 per cent, and 80 cubic centimeters of Rh negative blood were given. The baby received 75 cubic centimeters on October 11, 85 cubic centimeters on October 17, and on October 22, 80 cubic centimeters, for a total of 355 cubic centimeters of Rh negative blood. On October 24, the red cells were 3,600,000 and the hemoglobin 85 per cent. Following the last 2 transfusions the hemoglobin dropped in both cases. The baby was discharged from the hospital on the 21st day, and its condition was good. There is little doubt that the Rh negative blood in this case was incompatible. It was probably the means by which the baby's life was saved, however. The red cells remained in the circulation long enough to help the baby over the difficult period. The baby's serum and the mother's cells showed no agglutination. No antibodies could be demonstrated in the mother's blood. Had the cord transfusion with mother's blood been successful, there is no doubt the results would have been quite different.

CASE 9. Baby M., 32090. This patient was a secundigravida, 28 years old, Rh negative and her husband Rh positive. The patient had been operated on for a patent ductus arteriosus and had a severe reaction following a blood transfusion of Rh positive blood. Her own and her husband's blood were examined before her delivery by Dr. Levine; he found her husband Rh positive and Hr negative, so that all of the offspring would be Rh positive. The mother was immunized, as indicated by blocking antibodies. It was almost certain that the baby would be affected with erythroblastosis. The patient was delivered on March 24, 1946. The baby was given 40 cubic centimeters of Rh negative blood from a professional donor by cord transfusion. The baby was normal, with a red cell count of 7,940,000 and a hemoglobin of 140 per cent.

The following case is of interest. This baby received no transfusions.

CASE 10. Baby N., 31633. This is the only baby to be lost from erythroblastosis during the year 1945. The mother was 29 years old, a tertigravida, secundipara, Rh negative. The father, a daughter, and the baby were Rh positive. The baby's condition was good at birth; it was 39 weeks' gestation and weighed 6 pounds 2 ounces. It was slightly jaundiced. The spleen was palpable 17 hours after birth, the red cell count was 6,110,000 and the hemoglobin 120 per cent; there were only 2 normoblasts. When the baby was 2 days old it was still jaundiced, the spleen palpable and the blood count 5,940,000 and the hemoglobin 102 per cent. When the baby was 3 days old the red cells were 5,200,000 and the hemoglobin 90

TABLE VA.—ERYTHROBLASTOSIS, 9 BABIES TRANSFUSED WITH FATHER'S BLOOD

Year	Hospital No.	Age	Gravida	Living children	Normos.	R.B.C. 1st day	R.B.C. low	Hb. 1st day	Hb. low	Number of transfusions	Amt. of blood	Date of discharge	Jaundice	
1936	9394	30	iii	1	12	4.9	2.7	92	52	7	555	54	x	Died at 18 months
1936	17653	30	i		13	4.8	3.6	78	65	5	375	16	xxxx	Died from pneumonia 16th day
1936	15981A	36	vii	1	11	4.6	2.9	73	50	7	310	38	x	Labor induced at 8th month
1937	19093	23	i		2	5.9	3.5	104	75	2	140	12	.	Condition fair at birth. Spleen 1½ fingers below costal margin.
1941	19660	21	iii	1	69	5.6		97		2	90	2	xxx	Died. Spleen and liver enlarged at autopsy.
1941	12731B	36	iii	2	232	3.8		71		1	95	3	xxxx	Died. Spleen much enlarged at autopsy.
1941	5039B	38	vi	5	103	4.3	4.3	85	85	1	85	12		Many megaloblasts in blood smear.
1941	16312B	44	v	3	183	5.4	5.4	132	126	2	160	13		Mongolian. Died at about 8 mo.
1942	21878B	25	iii	1	627	3.6		79		2	155	2	xx	Pale, listless at birth. Died. 100 c.c. of Rh blood.

TABLE VB.—ONE BABY TRANSFUSED WITH BOTH FATHER'S AND MOTHER'S BLOOD

1941	24448	26	ii	1	276	4.3	3.4	78	54	4	230	12		Mother's blood by cord, 25 c.c. Father's blood, 75 c.c. Mother's blood, 50 c.c., 80 c.c. Total mother's, 155 c.c.

per cent. There was some occult blood on the diaper. At this time the baby was seen in consultation with Dr. Weiner, who diagnosed congenital hemolytic disease; he made this note: "If the hemoglobin drops to 80 per cent or below, 60 cubic centimeters of fresh citrated blood 'O' Rh negative, or washed cells from an equivalent amount of mother's blood should be given." During this day the baby became much worse, the jaundice much deeper and the spleen had considerably increased in size during the last 24 hours. The baby died that night without receiving a transfusion. There is little doubt that this baby would not have died had it received an early prophylactic transfusion of compatible blood.

CESAREAN SECTION IN RH NEGATIVE MOTHERS

In the group of 572 Rh negative mothers, there were 23 cesarean sections, 9 in the group of 232 transfused with mother's blood and 14 in the 340 either nontransfused or transfused with donor's blood. In the group transfused with mother's blood there was 1 death, the only case in which cesarean section was done prematurely to get a living baby; the gestation was 34 weeks. There were 2 other small prematures; 1 weighed 3 pounds 3 ounces and was of 36 weeks' gestation, and the other weighed 3 pounds 12 ounces. Both survived.

In the group not given prophylactic transfusions of mother's blood there were 2 infant deaths. In one, section was done for toxemia and the baby was stillborn. The other was of 39 weeks' gestation; it had 142 normoblasts and was transfused with 105 cubic centimeters of Rh negative donor's blood; death occurred on the second day. This is the first case reported in Table IV. One other baby in this group developed erythroblastosis; it was slightly jaundiced at birth, and following 2 transfusions of Rh negative blood recovered.

There were 18 low classical cesareans and 5 low cervical. Ten were primary and 13 secondary. There were no maternal deaths. There were no maternal deaths in the entire group of Rh negative mothers.

It has been recommended, if the mother has lost one or more children and is Rh negative, that a cesarean section be done at the eighth month in order to get a living child. I do not believe this is justified. If the baby is diseased you have not only a sick baby but also a premature one to deal with. As a rule the babies are in good shape at birth (see birth weights, Table III), but the disease develops rather rapidly, and if no transfusions are given the baby dies about the third day. Immediate transfusion given as a prophylactic measure is far preferable to the use of cesarean section to insure a living child.

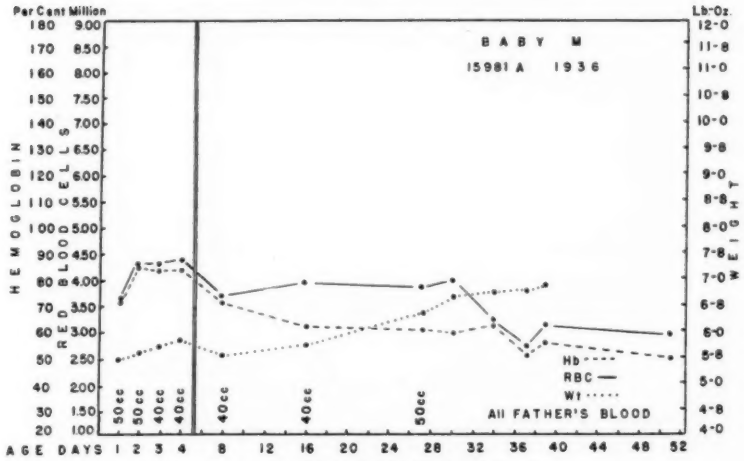

Fig. 4. Erythroblastosis fetalis. Case 11.

PREMATURE BABIES AND THE RH FACTOR

In previous articles (5, 6) I have stressed the importance of using mother's blood for a cord transfusion when the baby is premature. If the mother is Rh negative and the baby is born prematurely then we have double indication; the transfusion will benefit the baby if it is premature and will protect it if there should be any tendency toward the development of erythroblastosis. There were 35 babies premature either by weight or gestation who received transfusions of mother's Rh negative blood, with 7 deaths (Table IIA). Three of the babies were of 21 weeks' gestation or less; 2 died from congenital anomalies, 1 following cesarean section, of 34 weeks' gestation, mentioned, and the remaining 1 weighed 3 pounds 9 ounces and lived only 1 hour.

In the group of babies not receiving cord transfusions of mother's blood, there were 12 babies premature by gestation, 37 weeks or under, but only 5 by weight, 5½ pounds or under. Two of the babies died, 1 of 20 weeks' gestation and 1 of 34 weeks' which had a massive ventral hernia. The small number of cases in this group is explained by the fact that most of the prematures received cord transfusions.

TRANSFUSIONS WITH FATHER'S BLOOD

It is of some interest to compare the findings of the 3 year period studied with 10 cases that occurred between 1936 and 1942 in which father's blood was used (Table V). In 1936 nothing was known of the Rh factor, nor were we giving prophylactic transfusions of mother's blood to infants other than prematures unless the mother had lost one or more babies from erythroblastosis. There is little doubt that these 10 babies were suffering from some form of blood dyscrasia. Father's blood was used because in some cases the mother was not considered a suitable donor, the father's blood was easily obtainable and the relationship might make the blood compatible. In 9 cases father's blood was used with transfusion of donor's blood in 1 case; in the tenth mother's blood was given by cord transfusion, one transfusion of 75 cubic centimeters of father's blood on the 2nd day, and mother's in transfusions on the 5th and 9th days. The Rh factor was determined in only 2 of the 10 babies.

Of the 9 babies who received father's and donor's blood, 5 had more than 50 normoblasts; 4 more than 100 and 2 more than 200. Red cells were less than 4,500,000 in 4, and 7 had a hemoglobin of less than 100 per cent. Six were jaundiced, 2 markedly. The 9 mothers had a total of 23 previous pregnancies, with 14 living children. Seven were multiparas.

A total of 29 transfusions was given; 1 had a total of 5, 2 a total of 7. One baby was in the hospital for 38 days and 1 for 54 days.

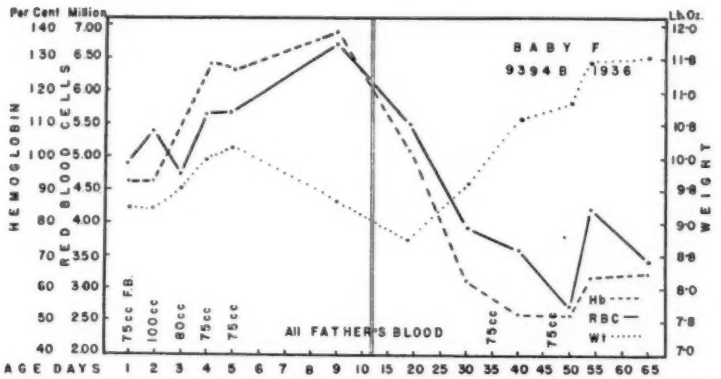

Fig. 5. Erythroblastosis fetalis. Case 12.

There were 4 deaths, and of the remaining 5, 2 died, 1 at 8 months, 1 at 18 months, leaving only 3 of the 9 to survive.

The infant given both mother's and father's blood did well; apparently the father's blood did not help the baby. This case, and 2 of the 9 cases in which father's and donor's blood was used, follow.

CASE REPORTS

CASE 11. Baby M., 15981A, (Fig. 4). This child's mother was a septigravida with 1 living child which was born in 1927. In 1928 a full term baby with icterus gravis lived for 2 days. The mother had stillbirths in 1929, 1931, and 1932. In 1935, because of her previous bad history, she was induced at the eighth month by the use of quinine and rupturing the membranes. The delivery was spontaneous; the baby weighed 5 pounds 5 ounces; it soon became weak and jaundiced, and died. In 1936 she was again induced at 37 weeks; the baby's color was good but slightly jaundiced. Four and one-half hours after delivery it received 50 cubic centimeters of its father's blood. The blood count on the day of delivery was 3,680,000 red cells, hemoglobin 73 per cent, and 11 normoblasts. The baby received 4 transfusions during the first 4 days of its life and on the 7th day the red cells were 3,740,000 and the hemoglobin 73 per cent. The baby received a total of 7 transfusions of father's blood and when it was discharged on the 38th day the red cells were 2,900,000 and hemoglobin 50 per cent. The baby now weighed 6 pounds 14 ounces.

CASE 12. Baby F., 9394, (Fig. 5). This mother was a tertigravida, 30 years old. She had a normal child in 1930 which was jaundiced. In 1935 she lost a baby which was very jaundiced, and the autopsy diagnosis was hemorrhagic disease of the newborn. In 1936 she was delivered of a full term baby weighing 9 pounds 3 ounces. The baby's condition was good at birth, but there was a slight yellowish tinge to the skin. The baby was given 75 cubic centimeters of its father's blood on the day of delivery when the blood count was 4,910,000 and the hemoglobin was 92 per cent. The baby was given 100 cubic centimeters of blood on the 2nd day, 80 cubic centimeters on the 3rd day, and 75 cubic centimeters on the 4th day, and 75 cubic centimeters on the 5th day. This baby had received 405 cubic centimeters of blood in 5 days. The blood count on the 9th day was 6,750,000 and the hemoglobin 138 per cent. By the time the baby had reached 30 days the red cells were 3,970,000 and the hemoglobin 63 per cent. At this time it received 75 cubic centimeters more of father's blood and when the baby was 7 weeks old the red cells were 2,700,000 and the hemoglobin 52 per cent. The baby received a total of 555 cubic centimeters of father's blood in 7 transfusions and was discharged at the age of 2 months. (It died later at 8 months.)

The father's blood in these 2 cases very likely saved the lives of these 2 babies, but there is no doubt that in the first case the blood was not compatible. If it had been compatible undoubtedly so many transfusions would not have been necessary.

CASE 13. Baby F., 24448, (Fig. 6). Mrs. F. was a secundigravida, primipara, 26 years old. She had a normal baby in 1937. On March 7, 1941, she was delivered of a female child weighing 6 pounds 4 ounces. At birth the liver was down to the umbilicus, but the spleen was not palpable. On the day of delivery the red cells were 4,320,000 and the hemoglobin 89 per cent, the white cells 358,000 and the normoblasts 276 per 100 white cells. There were many megaloblasts and marked polychromasia. The baby received 25 cubic centimeters of mother's blood by cord transfusion on the day of delivery, and on the following day there was an increase in the red cell count, the normoblasts had dropped to 138 and the

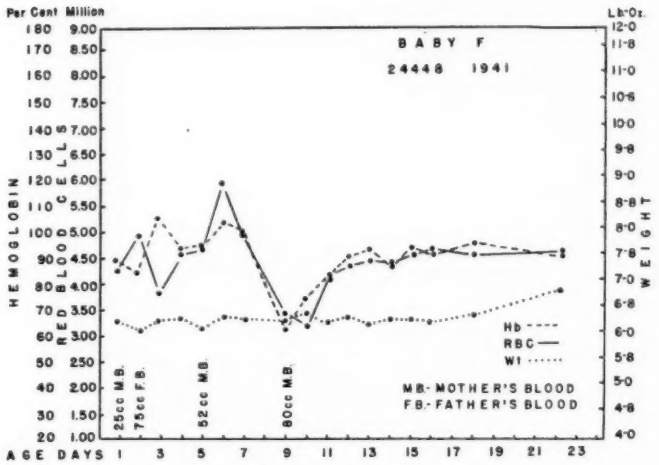

Fig. 6. Erythroblastosis fetalis. Case 13.

white cells to 178,000; 75 cubic centimeters of father's blood were given; following this the red cells dropped over a million cells. On the fifth day the baby was given 50 cubic centimeters of mother's blood and on the ninth day 80 cubic centimeters of mother's blood. The hemoglobin and red cells remained up, and when the baby was 20 days old the red cells were 4,500,000 and the hemoglobin 94 per cent. The baby weighed 6 pounds 12 ounces and was a normal baby.

In this case the father's blood did not help the baby, but the 2 following transfusions from the mother, who must have been Rh negative, were enough to keep the blood count at a satisfactory level.

ERYTHROBLASTOSIS IN INFANTS OF RH POSITIVE MOTHERS

A comparatively small number of the babies of Rh negative mothers develop erythroblastosis; of the 533 living infants of 572 Rh negative mothers delivered in a 3 year period, only 31, or 5.8 per cent, had erythroblastosis or some blood dyscrasia. The disease occurs even less frequently in infants of Rh positive mothers. Of the 5,917 Rh positive mothers delivered in the same period, only 6 of the babies had erythroblastosis, or it was suspected erythroblastosis might develop (Table VI).

Two of the 6 babies had more than 15 normoblasts; red cell count was less than 4,500,000 in 1, and hemoglobin less than 100 per cent in 1. Two of the mothers were primiparas. The 4 multiparas had had 12 previous pregnancies, with 3 living children.

Five of the babies were transfused with mother's blood, receiving a single transfusion. One received 3 transfusions of donor's blood, total amount 200 cubic centimeters. This baby had the longest stay in the hospital, 24 days. All recovered.

LITERATURE

Many articles have been written concerning the Rh factor in obstetrics and the great majority of them stress the importance of giving the baby of an Rh negative mother transfusions of "O" Rh negative blood. They also oppose the use of mother's breast milk.

Leonard reported from the New York Hospital 55 cases of hemolytic disease with a mortality of 34 per cent; 44 per cent of the babies had a nonspecific diarrhea. It is possible this might have been due to the fact that the babies were not breast fed and had difficulty in establishing proper intestinal flora. Two of the babies received transfusions of mother's blood when 5 to 7 days old; no ill effects were noted and there was an increase in hemoglobin. One hundred seventy-three transfusions of blood of an unknown Rh factor were given, and 80 to 90 per cent of these must have been Rh positive. In 2 cases death followed

TABLE VI.—INFANTS OF RH POSITIVE MOTHERS TRANSFUSED WITH MOTHER'S BLOOD OR DONOR'S BLOOD. BLOOD DYSCRASIAS SUSPECTED

Year	Hospital No.	Mother's age	Gravida	Living children	Normos.	R.B.C. 1st day	R.B.C. low	Hb. % 1st day	Hb. % low	Number of transfusions	Amt. of blood	Day of discharge	Birth weight	
1944	30169	21	i		53	6.3	6.2	150	150	1	75M*	12	6–14	Vernix yellow. Transfused in 8 hrs. Mother's blood used
1945	23924C	29	iv	1	32	6.9	6.2	144	120	1	45M	12	5–6	Husband Rh positive. Only living child had cord transfusion
1945	23715C	34	v	1	1	6.7		107		1	40M	13	6–11	Husband Rh pos. Only living child had a cord transfusion
1946	32182	32	iv	0	0	5.4		120		1	35M	12	6–6	Normal baby. Husband Rh pos. One baby died 6 mos. ges. Two full term lived only a few hrs.
1946	26880C	34	iv	0	1	7.6		147		1	50M	12	6–9	Normal baby. Husband Rh pos. 1945 Polyhydraminios. S.B.
1946	33171	20	i		0	4.2	3.7	99	96	3	200D	24	5–7	Parents and baby all Rh pos. This is the only baby in group receiving more than one transfusion

*M—mother's blood
D—donor's blood

the transfusion and may have been caused by it. Forty transfusions of Rh negative blood were given, and in 1 case the transfusion was followed by cyanosis, bloody nasal discharge, hematuria, and death in 48 hours.

Litchfield reported 3 cases of erythroblastosis in 1945. One of the babies, which was not transfused until it was 24 hours old, had 4 transfusions of Rh negative blood and 90 cubic centimeters of plasma from a compatible Rh negative donor. The baby stopped breathing following the transfusion of the plasma but was revived by artificial respiration and adrenalin. The baby died 24 hours later. The following note is made: "Despite the transfusions the infants became progressively worse. There is little doubt that transfusion reactions and factors other than the Rh prevented this infant from making a recovery." He reports that of 40 newborn infants who developed erythroblastosis, anemia or jaundice, 11 died.

Harville reported a case of erythroblastosis in which labor was terminated at the 8th month by cesarean section. Immediately following delivery the baby was given a cord transfusion of 60 cubic centimeters of Rh negative blood. The baby was given 2 more transfusions. The baby was normal in all respects. He comments as follows: "Cord transfusion, hitherto neglected in these cases, is an important adjuvant procedure in the management of the prematurely delivered erythroblastotic infant."

Rh positive blood can be used to treat erythroblastosis, according to Danis *et al.* if the red cells are concentrated by siphoning off the majority of the plasma. He also states that "we are impressed repeatedly with the results obtained with the use of father's blood. In many cases where the obstetrician had given one transfusion of father's blood before the patient came to us the results were quite remarkable."

Cold agglutinins described by Sanford and Gerstley accounted for the hemolysis following the use of Rh negative and Rh positive blood. At a temperature of 0 degrees Centigrade the cells would agglutinate, but at 20 or 30 degrees Centigrade there was no agglutination. He reports an infant recovering after 22 transfusions for a total of 2,300 cubic centimeters of blood over a period of 33 days.

If we are to judge from these reports and many others where reactions have followed the use of Rh negative blood, then it would seem that Rh negative blood from a donor other than the baby's mother must frequently be incompatible and at times its use causes such a severe reaction that the baby dies.

COMMENTS

Our experience at the Methodist Hospital, Brooklyn, has been quite in contrast to that of the great majority who have written about the Rh factor and its effect on the newborn. We have been led to believe that the Rh fac-

tor, although important in erythroblastosis, is not the exciting factor. If it were, certainly many more babies of Rh negative mothers would develop the disease. Moreover, if the anti-Rh agglutinins in the mother's blood cause the hemolysis in the baby's blood, we would be unable to give the mother's blood freely, as we have done.

Most of the babies in the cases reported nursed their mothers without any untoward symptoms. No one has proved that anti-Rh agglutinins in the mother's breast milk are absorbed from the infant's intestinal tract or that they are not destroyed by the intestinal ferments. The baby is apparently better off with its mother's milk, in spite of the anti-Rh agglutinins it may contain.

When blood other than the mother's is used for transfusion of the infant, there is a chance that the baby will be benefited. Reactions are quite common, however, and may be so severe that the baby will succumb during or soon after the transfusion. If the blood is incompatible there may be considerable loss in red cells and hemoglobin, but in spite of this the baby is temporarily benefited. Repeated transfusions, however, are necessary to keep the baby alive; even then, red cells and hemoglobin may not be increased because of incompatibility. Crossmatching to determine compatibility is impractical, since it is difficult to get sufficient blood from the baby unless blood is taken from the placenta at the time of delivery. Donor blood could be matched with that of the mother before the baby is born, and if compatible could be given by cord transfusion at delivery.

SUMMARY

1. During the years 1944, 1945, and 1946 at the Methodist Hospital in Brooklyn, Rh factor determinations were made in 7,032 women, and 1,042 or 14.7 per cent were found to be Rh negative.

2. In the same period, 572 Rh negative mothers were delivered. Somewhat less than half, 232, received transfusions of mother's blood, 229 by cord at birth, 3 later intravenously, with the loss of no viable baby from erythroblastosis. In the group of 340 not receiving mother's blood there were 5 deaths from erythroblastosis; 4 received donor's blood, 1 had no transfusion.

3. Comparison was made between the blood of 100 babies who received cord transfusions of Rh negative mother's blood and 100 babies not cord transfused with Rh negative mother's blood. The transfused babies had an average of 678,000 more red blood cells than the non-transfused babies.

4. A study of the compatibility of Rh negative mother's and baby's blood showed that in 80 cases there were only 10 in which there was any agglutination when the mother's cells and baby's serum was used. One baby, transfused with incompatible mother's blood, had no reaction.

5. A study of the compatibility of Rh positive mother's and baby's blood showed 6 in 46 cases in which agglutination occurred, when mother's cells and baby's serum was used.

6. There were 13 cases of erythroblastosis or suspected erythroblastosis in which transfusions of mother's blood were given, 10 by cord at birth, 3 intravenously later. There were no reactions and no deaths. These 13 infants all had some blood dyscrasia or the mother had a history of losing babies from erythroblastosis.

7. There were 17 babies with erythroblastosis transfused with blood of Rh negative group O, with the loss of 4 babies, in 3 of whom there was severe reaction. In 9 of the 17 more than 1 transfusion was necessary.

8. A brief report is made of father's blood given before the 3 year period reported; 9 babies received father's and donor's blood, 1 both mother's and father's blood. Of the 9, 3 died on or before the 3rd day, 1 on the 16th day; 2 died before their 2nd year, leaving only 3 survivors. A total of 29 transfusions was given. The 1 infant who received mother's and father's blood had 4 transfusions, 3 of mother's blood, 1 of father's, with no help from the father's blood. This infant survived.

9. Results obtained from Rh negative donor's blood and father's blood were somewhat similar. More reactions occurred immediately following transfusion in infants given donor's blood, but with both, more transfusions were needed and more deaths occurred. Apparent incompatibility was common.

10. There were 6 cases of possible blood dyscrasia with recovery in babies of Rh positive mothers. Five were given a single transfusion of mother's blood, 1 received 3 transfusions of donor's blood, with a total of 200 cubic centimeters. Four of the 6 mothers were multiparas and had lost 11 babies.

ADDENDUM.—We have transfused 31 additional babies using mother's Rh negative blood since January 1, 1947, there were no reactions and not one of the babies required a second transfusion. One of the babies had 40 normoblasts in the cord smear. This makes a total of 263 babies receiving mother's Rh negative blood with the loss of no babies from erythroblastosis.

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PATHOLOGICAL ASPECTS OF DEATH FOLLOWING MAJOR SURGERY

An Analytical Study of Postmortem Examinations of 57 Cases

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DEATHS following major surgery have been reduced to a low level in the general hospitals of this country in the past decade (1, 2). Improved surgical technique, good preoperative and postoperative care together with cautious selection of cases have all played a part in achieving the present low mortality rate following surgery. The surgeon, the internist, and the general practitioner are all directly concerned in the problem of death following major surgery. They are often called upon to evaluate the risk of surgery before operation and to anticipate the complications that may arise during surgery or in the postoperative period. It would seem logical to assume that one of the best ways for the physician to learn to make an accurate estimate of risk and learn to anticipate complications in individual cases would be to present an analysis of unselected postoperative deaths in general hospital surgical services and to analyze the anatomic lesions found at autopsy in these cases. The presentation is primarily from the standpoint of pathologic anatomy, but some clinical correlations have been attempted. Our plan is to present the statistical data without comment, then to discuss the data in the same order and finally to present a summary and conclusions.

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MATERIAL

All hospital deaths following major surgery in 2 general hospitals during the years of 1943 to 1945, inclusive were reviewed and those in which autopsy was performed were selected for analytical study. A few cases were excluded where permission for autopsy was partially limited, or where clinical data were so poorly recorded that correlation with pathologic findings was useless. Only those patients dying in the hospital during the same admission when surgery was performed, are included in this study.

PRESENTATION OF DATA

The total major surgical procedures recorded by the hospitals during the study period was 5,699. In this group there was a total of 138 deaths, or a total mortality rate of 2.4 per cent. In this group of 138 deaths there were 64 autopsies or an autopsy rate of 45.6 per cent. During the same 3 year period, the average autopsy percentage for all deaths occurring in the same hospitals was 50 per cent (Table I).

TABLE I.—SUMMARY—1943–1945, INCLUSIVE

Total major surgical procedures	5699
Total deaths after major surgery	138
Total autopsies on patients dying after major surgery	64
Autopsy percentage in above group of post-operative deaths	45.6
General autopsy percentage	50
Number of autopsy cases analyzed	57

TABLE II.—AGE OF PATIENTS

Age, years	No. of cases
Less than 1	2
1 to 9	0
10 to 19	3
20 to 29	1
30 to 39	1
40 to 49	7
50 to 59	7
60 to 69	17
70 to 79	10
80 and over	9
Total	57

Males, 31; females, 26.

A group of 57 cases in which postmortem examinations were made were selected for analytical study. These included 31 males and 26 females. The ages ranged from newborn to 89 years (Table II). The general types of operation are listed in Table III, together with the number of each. There were 19 different general classifications of surgical procedures and a total of 66 procedures on the 57 patients (since some patients had more than one procedure or more than one operation). There were 7 patients who had had more than one separate operation. Of the 57 patients operated upon, the operation was classed as an emergency procedure by the authors (after review of the clinical data) in 29 of the cases.

The anesthetic agents employed were cyclopropane, 35; ether, 2; pentothal sodium, 2; spinal (procaine), 3; local, 2; pentothal sodium and cyclopropane, 5; and other combinations of those noted, 8 (Table IV).

The number of days after surgery that death occurred is listed in Table V. One can see that 44 of the 57 deaths (77%) occurred within the first 2 weeks after surgery.

Study of the clinical records reveals that there were recorded preoperative and postoperative diagnoses in all but 3 cases, and that there was excellent agreement between preoperative, postoperative, and surgical pathological diagnoses, as shown in Table VI; however, the clinical records were found to be deficient when a search was made for a record of the clinical cause of death. No clinical cause of death was recorded in 31 cases. Of the 26 where some record of clinical cause of death was made, it agreed with the autopsy findings in 20 cases and disagreed in only 6.

TABLE III.—TYPES OF OPERATION

Type of operation	Number of patients
Enterostomy	13
Resection (bowel or stomach)	8
Exploration and biopsy	6
Hernia repair	5
Exploration and suture of perforated viscus	4
Exploration and drainage of peritoneal cavity	4
Suprapubic operations	4
Transurethral resections	4
Appendectomy	3
Cholecystectomy	3
Exploration and releasing of adhesions	3
Cholecystotomy	2
Amputation of penis	1
Pinning of fractured hip	1
Nephrectomy	1
Subtemporal decompression	1
Radical mastectomy	1
Interposition and vaginal plastic operation	1
Hysterectomy	1
Total	66*
Operation classed as emergency	29
More than one separate operation	7

*Some patients had more than one procedure or more than one operation.)

The actual analysis of autopsy findings was found to be difficult to present in a way that would have any meaning. We found immediately that a simple tabulation of major anatomic lesions found at autopsy was very unrevealing and confusing. For example, the heading "peritonitis" without individual case comment meant nothing and could refer to postoperative peritonitis due to error in surgical technique, or could mean perforation of a bowel carcinoma after simple exploration and biopsy. Also, for example, the heading

TABLE IV.—ANESTHETIC AGENTS

Anesthetic agent	Number of cases
Cyclopropane	35
Ether	2
Pentothal sodium	2
Procaine (spinal)	3
Procaine (local)	2
Pentothal and cyclopropane	5
Other combinations of above	8
Total	57

TABLE V.—DAY OF DEATH AFTER SURGERY

	Number of patients
Day of operation	4
First day after	6
Second day after	6
Third day after	3
Fourth day after	4
Fifth day after	4
Sixth day after	2
Seventh day after	4
8th to 14th day after	11
15th to 21st day after	5
22nd to 28th day after	3
Over 28 days after	5
Total	57

TABLE VI.—CLINICAL RECORDS

Chart record	Number of cases
Preoperative diagnosis recorded	54
Postoperative diagnosis recorded	49
Tissue removed and surgical pathological examination made	35
Preoperative or postoperative diagnosis agreed with surgical pathological diagnosis	26
Clinical cause of death recorded	26
Clinical cause of death agrees with pathological anatomy findings	20

"hemorrhage" might mean surgical hemorrhage or hemorrhage because of a primary disease unrelated to surgery. Thus, while we have listed the causes of death as recorded at autopsy (Table VII) we feel that this is of little value. Therefore, we tried to classify each death in a more analytical manner as due to (a) operative factors (shock, hemorrhage, peritonitis, evisceration, anesthetic) and (b) nonoperative factors (pulmonary embolus, heart disease, other new disease occurring in postoperative period, continuation of disease treated, diagnostic error with death from untreated disease). The division figures for each of these is given in Table VIII. These headings, while quite general, are much more revealing and meaningful from an analytical standpoint and serve to give a fair interpretation of the types of postoperative deaths based on postmortem studies.

The final item in this presentation of material and of figures deals with the incidental or other anatomic lesions found at autopsy, which are not included in Table VII because they were not concerned directly with the clinical postoperative course or the death of the patient. These so called "incidental findings" are given in Table IX.

TABLE VII.—MAJOR ANATOMIC LESIONS

General classification of cause of death	Number of cases
Peritonitis	14
Heart disease	12
Pulmonary embolus	10
Pneumonia	7
Carcinoma	6
Hemorrhage	4
Surgical shock	3
Urinary tract infections	3
Liver disease	3
Trauma (multiple wounds, etc.)	2
Mesenteric thrombosis or embolus	2
Mediastinitis (rupture of esophageal ulcer)	1
Acute hemorrhagic pancreatitis	1
Paralytic ileus (noninflammatory)	1
Acute ileitis (chronic ulcerative colitis)	1
Volvulus	1
Total	71

(Some cases are listed under more than one classification)

TABLE VIII.—ANALYTICAL CLASSIFICATION OF CAUSE OF DEATH

Operative factors		Nonoperative factors	
Peritonitis (surgical)	4	Heart disease	12
Hemorrhage	2	Pulmonary embolus	10
Shock	7	Other diseases developed in postoperative period	10
Evisceration	2	Continuation of disease treated	24
Anesthetic	0	Preoperative and postoperative diagnosis not made or in error and therefore, disease not treated	7
Total	15	Total	62

DISCUSSION

In discussing the data presented above, the first item deserving of comment concerns the total mortality figures of 2.4 per cent for the 5,699 major surgical procedures. This is somewhat difficult to compare with other studies because of the few published statistical data

TABLE IX.—IMPORTANT "INCIDENTAL" FINDINGS AT AUTOPSY APPARENTLY UNRELATED TO CAUSE OF DEATH

Incidental findings	Number of cases
Pulmonary tuberculosis (active)	2
Early cirrhosis of liver	2
Carcinoma of bronchus	1
Carcinoma of kidney	1
Glomerulonephritis (chronic)	1
Focal pancreatic necrosis	1
Bronchiectasis	1
Chronic lymphatic leucemia	1
Total	10

TABLE X.—CARDIAC DEATHS

Case	Clinical heart disease preoperative	Age	Clinical hypertension	Heart weight (gm.)	Grade of coronary artery I–IV sclerosis	Pathologic anatomy (heart only)	Emergency operation
1	Yes	52	No	480	I	Chronic rheumatic mitral endocarditis with stenosis; auricular thrombosis	Yes
2	No	87	Yes	465	III	Hypertrophy; dilatation; focal fibrosis of myocardium	Yes
3	Yes	77	Yes	410	II	Calcareous aortic stenosis; marked dilatation	Yes
4	Yes	58	No	450	II	Hypertrophy; dilatation; auricular thrombosis (left)	No
5	Yes	70	Yes	375	III	Rt. ventricle hypertrophy; dilatation large fibrous scar of myocardium	No
6	Yes	71	Yes	580	III	Marked hypertrophy and dilatation; old infarction of myocardium	No
7	No	68	No	500	II	Old coronary occlusion; fibrous scar l. apex; aneurysmal dilatation l. ventricle apex; mural thrombosis l. ventricle	Yes
8	No	52	?	500	III	Marked hypertrophy; dilatation l. ventricle	Yes
9	?	80	?	350	III	Acute infarction of myocardium	No
10	Yes	72	Yes	530	III	Hypertrophy; dilatation; old atheromatous coronary occlusion; myocardial scar, mural thrombosis	No
11	?	84	Yes	500	III	Marked hypertrophy. Terminal l. ventricle dilatation	Yes
12	Yes	67	Yes	450	II–III	Old coronary occlusion; fibrosis of myocardium; hypertrophy and dilatation	Yes

of this type that we have been able to find. Most data concern mortality rates for certain selected operative procedures or special groups of patients. Also the designation of *major* surgical procedures varies somewhat in different institutions. One report from a 600 bed hospital (2) with 250 general surgical beds gives a range of from 2 per cent to 3 per cent operative mortality after 3,509 to 4,233 major operations. This, however, does not include all postoperative deaths as they exclude so called nonoperative deaths occurring in the postoperative period. Another report from a small hospital (1) of less than 100 beds, and including 785 major operations over a 6 year period gives a total postoperative mortality rate of 3.9 per cent. Certainly our figures are all inclusive for deaths in the postoperative period and apparently reflect a rather low total mortality rate.

The figure of 45.6 per cent autopsies in these 138 postoperative deaths as compared with an overall autopsy rate of 50 per cent for all deaths is rather interesting. One frequently finds isolated cases in which patients die in the postoperative period and in which autopsy is refused because the operation has already revealed the nature of the disease process or because the surgical procedure is blamed by the family for the fatal outcome, or rarely, because of passive resistance on the part of the surgeon. Since these isolated cases tend to be remembered longer, we had anticipated a lower autopsy percentage among postoperative deaths; the figures are only slightly lower, however, than for the general autopsy statistics.

The ages of our patients are probably quite indicative of age distribution of patients undergoing general surgery with perhaps some accentuation of older age groups since they would be expected to exhibit a higher mortality rate. Forty-three of the 57 deaths were in patients 50 years of age or older. Nineteen were 70 years or older.

The list of various surgical procedures carried out on the 57 patients studied reveals a fairly wide range of general surgical material. The most frequent surgical procedure followed by death in this study came under the general heading of enterostomy (colostomy, cecostomy, ileostomy, etc.). As might be expected these procedures were done for relief of intes-

TABLE XI.—DEATHS FROM NONSURGICAL DISEASES APPEARING IN POSTOPERATIVE PERIOD EXCLUDING HEART AND PULMONARY EMBOLUS

Disease	Number of cases
Pneumonia	6
Chronic duodenal ulcer with hemorrhage	1
Portal cirrhosis	1
Subacute yellow atrophy of liver	1
Carcinoma of lung	1
Total	10

tinal obstruction, often due to malignant neoplasm and sometimes accompanied by resection of a portion of gastrointestinal tract. The resection group was the second largest group, followed by combined exploratory laparotomy and biopsy.

In this phase of the discussion, we feel that it is important to point out the fact that in 57 deaths, 7 had had more than one separate operation during their hospitalization. This does not include multiple procedures done at one time (such as bilateral hernia repair; cholecystectomy and appendectomy etc.), but operations done on different days. Some were part of multiple stage procedures, some elective multiple operations, and others were reoperated upon because of some difficulty arising after the first operation (not including two eviscerations). It would seem that this figure of over 12 per cent of the total postoperative deaths having more than one surgical procedure would point out a definite hazard, and one which many times could be eliminated by choice.

Along the same line is the fact that 29 of the 57 (51%) were classed as emergency procedures by the authors after review of the clinical records. Using the definition that an emergency is "an unforseen circumstance that necessitates immediate action to attempt to save life," there probably is little that can be done to eliminate this hazard. However, the immediate action taken doesn't always have to be surgery. Judicious use of conservative means in an effort, first, to carry out the laboratory and clinical tests necessary to obtain a more definite diagnosis, and second, to administer supportive therapy methods to get the patient in as good condition preoperatively as possible, will always be justified. The pathologist rarely does an autopsy on a patient who dies because an operation was too long delayed (i.e. few hours to few days), but he frequently sees the poor results from operations attempted before adequate diagnostic methods, conservative and supportive therapeutic measures have been carried out. Of necessity, some situations demand immediate operation and also of necessity, some surgery must be done without a definite diagnosis, but our study shows that this "emergency group" comprises over half of the postoperative deaths in which autopsies were done and therefore points the way to caution.

Since there were no deaths attributed primarily to anesthesia, no comments regarding anesthetic agents will be made other than those given in Table IV.

The number of days after surgery when death occurred is given in Table V. Forty-four, or 77 per cent occurred within the first 2 weeks after surgery. We have no further comment to make on this fact.

The study of clinical records deserves only brief comment. Most were found quite complete except for lack of written note regarding the *clinical cause of death.* This is an important omission, for the clinician has thus missed an opportunity to test his diagnostic acuity and has failed to record in the chart evidence of his interest in the case even though the outcome was unfavorable. He has not given the pathologist a prenecropsy statement as to what problems he specifically is concerned with and thus perhaps makes the autopsy less revealing. This is an omission of recording that can easily be remedied to the advantage of all concerned.

In discussion of the causes of death as listed under the general headings of operative factors and nonoperative factors (Table VIII), it is striking to note the relatively few operative factors. The subheadings under this group are quite clear cut and need no detailed comment. Many were present in combination with nonoperative factors.

The various subdivisions under nonoperative factors will be considered in some detail. The first heading of *heart disease* consists of 12 cases in which the autopsy findings indicated that heart disease was the immediate or chief

cause of death or at least one of the major factors in death. More detailed information regarding these cases is given in Table X. The one thing that stands out most prominently is the occurrence of a combination of cardiac hypertrophy and rather severe coronary arteriosclerosis in 8 of the 12 cases. While a high incidence of coronary arteriosclerosis might be anticipated in this age group, it would appear that the presence of the two was a definite hazard in the group of postoperative deaths studied. In addition to the 12 cases tabulated in Table IX, there were other evidences of cardiovascular disease in several others of the entire group of 57 cases. Excluding the 12 referred to, there were 8 additional cases in which the heart was definitely hypertrophied at autopsy (450 grams or more), 7 additional cases in which coronary arteriosclerosis was grade III or more (2 with both hypertrophy and coronary sclerosis) and 9 additional cases in which there was clinical hypertension. In all, there were 16 patients in addition to the 12 primary cardiac deaths that had either cardiac hypertrophy (over 450 grams) coronary sclerosis of at least grade III, clinical hypertension, or some combination of the three. This makes an overall total of 27 patients, or 49 per cent of those dying after major surgery, who had clinical or anatomic evidence of cardiovascular disease.

The next item under nonoperative factors is that of pulmonary embolus. There were 10 cases in which pulmonary emboli were present. Five of these were uncomplicated by any other significant findings and 5 others were found in association with other factors considered definitely related to the patients' deaths. The 5 deaths due entirely to massive pulmonary embolus occurred 6, 10, 12, 13, and 17 days after surgery.

Under the heading of *other disease*, occurring in the postoperative period we have listed 10 cases. Some of the disease processes were undoubtably present before surgery, but are included in this group. Table XI lists the chief features of this interesting group of postoperative deaths. Six were pneumonias of severe type and serve to stress the fact that some pneumonias in the postoperative period do not respond to chemotherapy. In one interesting case in which the patient died less than 24 hours after surgery there was found such extensive pneumonia with abscesses that it was apparent that the process had been present before the operation. The case of hemorrhage from a large chronic duodenal ulcer (occurring during patient's convalescence from nephrectomy) serves as a most pointed example (as do all these nonoperative deaths), that a single history and physical examination on admission to a hospital may not be all revealing. It should never be assumed that because a patient does poorly after surgery that the cause is directly related to his operation. A fresh start and reconsideration of the case as if it were a new admission is sometimes indicated.

TABLE XII.—DEATHS FROM UNTREATED DISEASES DUE TO DIAGNOSTIC ERROR OR NO DIAGNOSIS MADE

Apparent clinical diagnosis	Pathologic anatomy	No. of cases
Acute intestinal obstruction	Perinephric abscess—ileus	2
Acute appendicitis	Mesenteric thrombosis	1
Mesenteric thrombosis	Volvulus—early strangulation	1
Perforated duodenal ulcer	Perforated esophageal ulcer	1
Obstructive jaundice	Hepatitis and early cirrhosis	1
Probable strangulated hernia	Post-traumatic ileus (fracture lumbar vertebra)	1
	Total	7

The group of cases listed as *continuation of the disease treated* needs very little comment. It includes that large group of palliative surgical procedures in the noncurable stage of carcinoma and those unsuccessful attempts to save life in mesenteric thrombosis, acute hemorrhagic pancreatitis, severe trauma, etc.

Finally we have 7 cases in which it appeared from the records that preoperative and operative diagnoses were not definitely made or were in error and death was due to continuation of untreated disease, i.e., untreated because not diagnosed. In some of these cases the patients were almost *in extremis* when admitted and no opportunity for adequate study was possible, yet it appeared that surgery was justified. Some of these represent the most difficult diagnostic problems and are listed factually with no intent to criticize. Table

XII lists the apparent clinical diagnosis first and opposite this the anatomic findings as revealed by autopsy. Fortunately, these cases are uncommon, but the occurrence of 2 cases of perinephric abscess, due to long standing renal lithiasis and pyenephrosis presenting themselves for the first time with signs of acute intestinal obstruction shows the diagnostic difficulties offered to the clinician and surgeon.

In concluding this discussion we refer to Table IX which lists so called "incidental findings," unrelated directly to the cause of death. These findings sometimes are more important to the survivors of the deceased than the other observations, and in the cases of pulmonary tuberculosis may actually be of prophylactic value. It serves to stress the fact often overlooked that the purpose of the autopsy is not alone to determine the cause of death, but also to record evidence of past diseases and of those diseases which might have been yet to become active had the patient lived.

SUMMARY AND CONCLUSIONS

1. The risk of death following major surgery in this community is low and apparently compares favorably with reported incidences of postoperative deaths from other institutions.

2. Autopsy percentage in postoperative deaths is nearly as high as in all hospital deaths in this community.

3. This group of postoperative deaths includes a relatively large number of so called emergency procedures and also a relatively large number of patients submitted to more than one operative procedure at a single hospitalization. These observations suggest that reasonable delay in an effort to make a more accurate diagnosis and to allow time for general supportive therapy is justified. It would appear that multiple elective procedures at one hospital stay is an avoidable hazard.

4. There are relatively few deaths in this group due to purely operative or technical factors and none primarily due to anesthesia.

5. Most deaths in this study were due to nonoperative factors and while heart disease, pulmonary embolus, and unsuccessful removal of pathological processes by surgical methods accounts for most of these, there are some deaths due to other diseases which developed or occurred in the postoperative period or which were undiagnosed at operation and tax the diagnostic ability of surgeon and clinician. A recheck of the postoperative patient who is not doing well, with the thought in mind that there may be present a disease process wholly unrelated to surgery would undoubtably yield much information.

6. Nearly one-half of the patients dying after major surgery in our study had clinical or anatomic evidence of cardiovascular disease. Except for an indication that coronary arteriosclerosis combined with cardiac hypertrophy is a hazard, this study helps very little to solve the question of which cases of compensated cardiac disease, if any, should avoid elective surgery.

7. One deficiency in clinical records was the lack of any recorded statement in regard to the clinical diagnosis of cause of death. The importance of this omission is discussed.

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A STUDY OF SYSTOLIC BLOOD PRESSURE AND PULSE RATE IN TRAUMATIC SHOCK

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IN the conventional description of the clinical picture of traumatic shock prevalent in textbooks and medical literature, the systolic blood pressure is recorded as "low" and the pulse rate as "rapid." A value of 80 or below for systolic blood pressure is often taken as indicative of shock following trauma and the pulse rate is expected to be correspondingly elevated. In a fairly large civilian and military surgical experience the authors have come to believe that the clinical features of the state of traumatic shock are considerably less constant than is usually supposed. One or more of the characteristic clinical findings, considered as having diagnostic and prognostic value, may be absent in a patient whose condition in general presents unmistakable evidence of the state of traumatic shock. The conclusion is forced upon one that the essential disturbances of the condition, such as reduction in cardiac output, reduction in peripheral blood flow and tissue anoxia, are not always accompanied by the same signs. In fact, the essence of the state of traumatic shock would seem to lie in the labile and transitory nature of the adjustments achieved by the organism, and variation rather than constancy should be expected in its clinical manifestations. The point is of more than academic interest, both to physiologists and clinicians. Accordingly it seemed worth while to attempt an evaluation of two of the reactions which are widely regarded as of critical interest in the diagnosis and prognosis of shock, namely, the systolic blood pressure and the pulse rate. Rather complete notes on a group of severely wounded soldiers afforded suitable data for assay.

Detailed and careful personal observations had been made on several hundred seriously wounded soldiers, treated as nontransportable casualties at forward field hospitals. From these cases 204 were selected for study, all suffering from penetrating or perforating wounds from high explosive missiles, and all presenting the clinical picture of actual or imminent shock. All had grave wounds of chest, abdomen, major bones and joints, or combinations of these wounds. The amounts of plasma and blood given at various intervals had been recorded, as well as the time between wounding and admission to field hospital, the time between admission and surgical operation, and

TABLE I.—PLASMA AND BLOOD ADMINISTERED TO 204 GRAVELY WOUNDED SOLDIERS AND TIME INTERVALS

Intervals			Plasma			Blood		
	No. of observations	Average minutes	No. of observations	Number receiving plasma	Average am't received c.c.	No. of observations	Number receiving blood	Average am't received c.c.
Wounding to admission	203	350	204	109	650	204	5	500
Admission to operation	204	221	204	132	640	204	156	990
Operation	197	135	201	62	560	201	162	898

TABLE II.—MORTALITY DIVIDED ACCORDING TO INITIAL SYSTOLIC BLOOD PRESSURE ON ADMISSION TO FORWARD FIELD HOSPITAL

	Number cases observed	Deaths	Mortality rate % (31/204)
Admission systolic blood pressure over 100	78	4	5.1
Admission systolic blood pressure 51–100	92	17	18.5
Admission systolic blood pressure 50 or less	17	4	23.5
Admission systolic blood pressure zero	13	6	46.2
All cases*	204	31	15.2

*In 4 instances systolic blood pressure at admission was not recorded, but in none of the 4 cases was the outcome fatal.

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TABLE III.—SYSTOLIC BLOOD PRESSURE AND PULSE RATE IN 31 FATALLY WOUNDED SOLDIERS

Time	Systolic blood pressure				Pulse rate			
	No. of observations	High	Low	Average	No. of observations	High	Low	Average
At admission	31	150	0	63.8	18	160	48	119
Before operation	31	140	0	98.3	29	170	60	138
At end of operation	28	138	0	87.6	26	150	60	120

The average time intervals for the group were, from wounding to admission to forward field hospital 251 minutes; from admission to operation 287 minutes; from beginning to end of operation 149 minutes.

the duration of operation. As noted elsewhere there is good reason to believe that the major cause of the state of shock in such fresh casualties is blood loss (1, 2). As shown in Table I the wounds were recent at the time the casualties were admitted to the field hospitals for treatment, the average interval between wounding and admission being just under 6 hours. The gravity of the wounds is attested by the amounts of plasma and blood considered necessary in preparation for and in conduct of surgical operation. The men were for the most part previously healthy young soldiers, the average age being 24.6 years and the oldest being 42.

For the entire group of 204 casualties, there were 31 deaths during the forward observation

TABLE IV.—SYSTOLIC BLOOD PRESSURE AND PULSE RATE IN 204 CASES

Time	Systolic blood pressure		Pulse rate	
	No. of observations	Average value	No. of observations	Average value
At admission	200	88.6	140	109.0
Before operation	200	120.4	194	123.6
At end of operation	200	110.8	190	115.9

period. If the cases are divided according to initial systolic blood pressure readings at admission to hospital, as shown in Table II, it is seen that some correlation appears to exist between degree of hypotension and prognosis. Exceptions are fairly numerous, however. The mortality rate of 15.2 per cent for the entire group indicates the severity of the wounds under consideration.

The data of Tables III and IV bear on the question of the prognostic value of changes in systolic blood pressure and pulse rate in the wounded. It is seen that the average values for systolic blood pressure are consistently lower at the three points of observation in the fatal cases as compared with the entire group, and the average values for pulse rate consistently higher. However, as systolic blood pressure rises preoperatively under restorative therapy, so does pulse rate as portrayed in Chart 1. Systolic blood pressure and pulse

TABLE V.—CORRELATION OF SYSTOLIC BLOOD PRESSURE AND PULSE RATE AT DIFFERENT INTERVALS IN THE EARLY CARE OF GRAVELY WOUNDED SOLDIERS

	Observations at admission			Observations before operation			Observations at end of operation		
	Pulse rate			Pulse rate			Pulse rate		
	0–80	81–100	Over 100	0–80	81–100	Over 100	0–80	81–100	Over 100
	No. of observations	No. of observations	No. of observations	No. of observations	No. of observations	No. of observations	No. of observations	No. of observations	No. of observations
Admission systolic blood pressure over 100 (78 cases)	8	29	21	4	21	49	3	16	56
Admission systolic blood pressure 51–100 (92 cases)	2	9	55	1	14	73	2	14	68
Admission systolic blood pressure 1–50 (17 cases)	1	0	10	1	1	14	1	4	10
Admission systolic blood pressure 0 (13 cases)	0	1	2	1	2	9	0	4	8

The pulse rates are for the same group, as classified according to admission blood pressure, followed throughout the periods of observation.

rate both show a decline during the period of surgical operation. A rising pulse rate under treatment for shock does not appear to have prognostic significance, if average values are considered. Furthermore, as systolic blood pressure rises toward the normal, pulse rate becomes increasingly abnormally rapid. Accordingly the value for systolic blood pressure in a given case would seem to be a much better index of the patient's condition than pulse rate.

The values for systolic blood pressure and pulse rate as classified for the entire group studied are shown in Table V as the basis for computing correlation between these two factors. The values are taken at three points of observation, namely, at admission to the hospital, immediately before operation, and immediately after operation. If coefficients of correlation between systolic blood pressure and pulse rate are computed by the product-moment method using Pearson's formula, we find that:

1. For admission observations $r_1 = -.36$ for 140 cases.
2. For observations before operation $r_2 = -.21$ for 194 cases.
3. For observations at end of operation $r_3 = -.10$ for 189 cases.

If it is recalled that a value of 1.0 for r indicates perfect correlation and that a zero value indicates total lack of correlation, it is clear that no significant correlation can be discerned between systolic blood pressure and pulse rate. Furthermore, the coefficient of correlation becomes progressively lower under treatment. In order to demonstrate that this decrease in the value of r represents a significant trend and is not merely a chance finding the critical ratios between r values are determined. It is found that

C.R. for $r_1 - r_2 = 2.2$
C.R. for $r_2 - r_3 = 1.7$
C.R. for $r_1 - r_3 = 3.8$

A critical ratio of 3.0 or above is highly significant and the above values therefore support in substantial degree the conclusion that changes in systolic blood pressure and pulse rate in this study are quite poorly correlated.

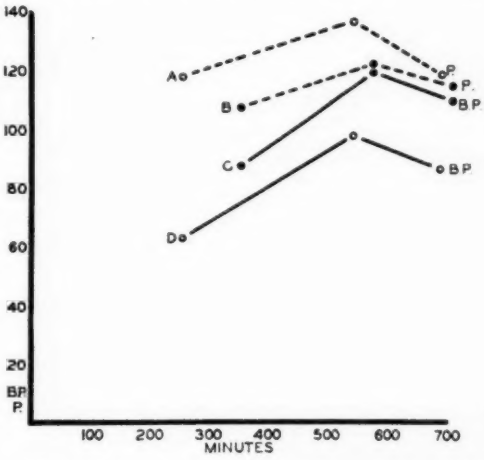

Chart 1. A study of systolic blood pressure and pulse rate in traumatic shock. *A*, Pulse versus time after wounding in 31 fatal cases; *B*, in 204 severely wounded cases. *C*, Systolic blood pressure versus time after wounding in 204 severely wounded; *D*, in 31 fatal cases.

SUMMARY

1. Values for systolic blood pressure and pulse rate in 204 freshly gravely wounded soldiers have been examined.

2. In nonfatal as well as fatal cases the systolic blood pressure under restorative therapy tended to rise toward normal, whereas the pulse rate tended to rise away from normal.

3. Coefficients of correlation between systolic blood pressure and pulse rate are shown to be quite low both before and after restorative therapy and surgical operation.

4. Systolic blood pressure appeared to have more prognostic value than pulse rate, though both showed more deviation from the normal in fatal cases than in the group as a whole.

5. Systolic blood pressure and pulse rate in traumatic shock should be considered as representing the momentary effect of varied and compounded physiological reactions. The frequency of exceptional values indicates that these two factors require caution in the evaluation of the state of traumatic shock.

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INDICATIONS FOR SIMPLE MASTECTOMY

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THE operation of "simple mastectomy" may be performed as a therapeutic or as a prophylactic procedure. It should not be utilized as a diagnostic method. Unfortunately these distinctions are not always clear in the minds of many surgeons, and considerable surgical abuse of the female mammary gland results. Lack of understanding of breast pathology and the physical harmlessness of even major breast surgery are factors contributing to the casual sacrifice of this organ. The mortality from breast surgery is practically nil, and the physiological effects of removal of one or both mammary glands are likewise negligible, considering modern pediatric facilities. Nevertheless, conservation of tissue, and avoidance of unnecessary destruction, would seem to be fundamental surgical principles. Applied to surgery of the mammary gland such a principle is valid in itself, aside from the important psychological and financial considerations incident to removal of a breast.

Bloodgood's succinct remark that a simple mastectomy is too radical a procedure for benign lesions and inadequate for malignant tumors is correct in principle but would seem to be too dogmatic a condemnation of this operation. In view of the confusion that seems to exist about the indications for this surgical procedure, we have reviewed the cases seen in the tumor clinic of the Research and Educational and the Presbyterian Hospitals in an attempt to clarify the rationale for performing a simple mastectomy. These patients are referred to the tumor clinic from the entire state and probably represent a fair cross-section of medical practice. Seventy-one such patients have been reviewed and are the basis of this report.

ANALYSIS OF CASES

I. Simple mastectomies for diagnosed breast lesions 21
   a. Carcinoma 9
      (Palliative 3)
      (Poor risk 6)
   b. Precancerous lesions 5
      (Previously diagnosed by biopsy)
   c. Mastodynia 2
   d. Papillary cystadenoma 1
   e. Recurrent, multiple cystosarcoma phyllodes 1
   f. Multiple, persistent draining sinuses 1
   g. Tuberculosis of breast 1
   h. Liposarcoma 1

II. Simple mastectomies for lump in breast 33
   Pathology
   a. Carcinoma 13
      (6 converted to radical)
   b. Chronic cystic mastitis 16
   c. Papillary cystadenoma 2
   d. Solitary cyst 1
   e. Fat necrosis 1

III. Simple mastectomies for bleeding nipple 14
   Pathology
   a. Chronic cystic mastitis 10
   b. Intraductal papilloma 3
   c. Carcinoma 1

IV. Simple mastectomies for eczema of nipple ... 2
   Pathology
   a. Eczema 1
   b. Paget's disease 1

V. Simple mastectomies for clear discharge from nipple 1
   Pathology
   Chronic cystic mastitis.

Group I. Twenty-one patients of this group had "simple" mastectomies performed after a diagnosis had been established either by biopsy or clinical recognition of an obvious lesion.

a. Nine operations were done because of cancer, 3 of which were deliberately palliative for lesions considered incurable. These were large ulcerated and fungating masses. The other 6 patients with cancer were such poor surgical risks due to age or cardiovascular disease or both that a radical mastectomy was deemed inadvisable. Aside from the increased surgical risk there is no point in trying for a "five year cure" in an elderly patient whose physical condition can only give a reasonable life expectancy of 2 to 3 years. This, of course,

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requires careful evaluation, as one must not err on the side of conservatism in treating cancer.

b. Five of the patients in group I had a simple mastectomy performed because of a previous biopsy diagnosis demonstrating a lesion considered to be "pre-cancerous." It is significant that, in the total series of 71 cases, only 5 were considered to be precancerous. This is the most controversial question in breast pathology and will be discussed later.

c. Two patients had simple mastectomy done because of such severe pain in one breast that they were literally in danger of becoming narcotic addicts. We have no explanation of this degree of mastodynia, but it was not on a neurotic basis in these instances nor were they actual addicts, as both patients were completely relieved. Each had had one or more excisions of painful areas of chronic cystic mastitis before mastectomy, and neither had been relieved by hormone therapy.

d. This patient had multiple excisions of benign papillary cystadenomas, and had multiple tumors when seen in the clinic. The other breast was unaffected. It was obvious that only a mastectomy here could obviate a potentially dangerous situation.

e. This patient had multiple, recurrent, "miniature" cystosarcoma phyllodes and a mastectomy was the only recourse.

f. and g. These two groups are self-explanatory and comprise 2 patients, in each of which the breast was irreparably damaged by abscesses and chronic draining sinuses.

h. This patient had a bulky liposarcoma, diagnosed on biopsy, and an extensive, complete mastectomy was performed without removal of pectoral muscles or axillary contents.

Group II. In this group there are 33 patients who had a simple mastectomy performed because of the presence of a mass in the breast. In some of these patients it is probable that the surgeon suspected carcinoma. None of these patients, however, were in too poor physical condition to tolerate a radical mastectomy, nor were the cancerous lesions advanced when first operated upon.

a. Thirteen patients of this group had carcinoma of the breast and all but two had recurrences when seen in the clinic. These 2, and 4 others who were still operable, were reoperated upon and the surgical therapy converted to a radical mastectomy. The other 7 patients were candidates for palliative radiation only.

b. Sixteen patients of this group showed only chronic cystic mastitis in the amputated breasts. The types of mastitis present were not considered significant or necessarily indicative of possible future trouble. Most of these patients were under the age of 40 years.

c, d, and e. The breasts of 2 patients showed benign papillary cystadenomas, one specimen showed only a solitary cyst of the "blue-dome" type, and one showed only fat necrosis from a previous injury. This last diagnosis was suspected before operation, but the surgeon did a simple mastectomy.

Group III. Fourteen patients were subjected to simple mastectomy because of the history of bloody discharge from the nipple. Only one of these had a discrete mass in the breast. This was in a senile patient whose operation was performed under local anesthesia because of her poor physical condition. The mass was minute and pathologically was a low-grade intraductal papillary carcinoma with beginning infiltration of the duct wall. Three cases of benign intraductal papillomas were found. None of these showed atypical cytological changes. Ten of the specimens showed only varying degrees of chronic cystic mastitis of no particular prognostic significance.

Group IV. In this group 2 patients were subjected to simple mastectomy because of the presence of eczema of the nipple. The specimen from 1 patient, 31 years old, showed only eczema. This same patient developed eczema of the remaining nipple several years later, and this promptly subsided under dermatologic care. The other patient had true Paget's disease and in the amputated breast there was also a focus of infiltrating duct carcinoma which was palpable before surgery was performed.

Group V. One patient is listed who had a simple mastectomy because of a clear discharge from the nipple. No discreet mass was palpable. The breast specimen showed only chronic cystic mastitis of no particular significance.

RÉSUMÉ

From this review it would seem that in 71 instances of simple mastectomy, only 21 were justified. These 21 cases were all direct attempts at eradication of a known disease, and in each, the diagnosis had been established either by biopsy or clinical recognition of an obvious lesion. These 21 cases comprised 9 of carcinoma, 5 diagnosed as precancerous lesions, 2 of uncontrollable mastodynia, and 1 each of recurrent and multiple papillary cystoadenomas, multiple recurrent cystosarcoma phyllodes, tuberculosis of the breast, liposarcoma of the breast, and chronic draining sinuses of the breast with destruction of the gland.

Six of the patients treated for cancer were such poor surgical risks that only a simple mastectomy was considered justified. Two are untraced, 2 are dead of heart disease, and 2 are alive over 2 years without evidence of recurrence. The 3 patients treated by simple mastectomy as a palliative procedure had varying histories. One had recurrence in the scar in 3 weeks, 1 was dead in 3 months, and 1 is alive and well 8 years. This last is obviously a case of mistaken prognostic estimate as the microscopic sections have been reviewed and verified. Simple mastectomy is useful as a palliative operation to remove bulky, ulcerated, and fungating masses. Ordinarily x-ray treatment would be expected to follow such a procedure. In many such cases a radical mastectomy will give better palliation than a simple, if the lesion is locally operable and axillary metastases are not fixed. The palliative value of a radical mastectomy has not been adequately appreciated or publicized. Actually most radical mastectomies are palliative, in the sense that less than half of all breast cancers so treated are cured, although the operation originally was advised as a curative attempt.

The other cases considered to be valid indications for simple mastectomy are largely self-explanatory. The 5 patients who had simple amputation following microscopic diagnosis of a precancerous lesion had diffuse duct changes that were considered to be dangerous enough to warrant extirpation of the breast. Their number in this series is small, but their number is minute compared to the hundreds of patients having had radical mastectomy and patients having only local excision of benign lesions passing through the tumor clinic.

The 50 patients in this series whose simple mastectomies are considered to have been unnecessary are probably mainly overzealous attempts to be on the safe side. Simple excision of the mass, however, would have accomplished the same thing, and in the cancer cases would have afforded less temptation to temporize with the disease. It would seem unnecessary to comment on the seriousness of the error in removing a breast of a younger woman for a benign lesion, or, equally, the error of inadequate surgery for a malignant tumor.

It may be argued that the simple mastectomies done for chronic cystic mastitis were justified from the standpoint of prophylaxis of later cancer, yet the 26 cases listed in Groups II and III were not considered to show precancerous changes. Indications for simple mastectomy are fairly clear when a definite known disease entity is being treated, such as cancer in a poor risk patient, tuberculosis of the breast, or cystosarcoma phyllodes. It should be equally clear that this surgical procedure should not be used for diagnostic purposes. The prophylactic aspect of prevention of breast cancer, however, is a very controversial subject.

The conflict lies, of course, in the definition of what is, and what is not, a "pre-cancerous" lesion. If we could be certain that a given breast lesion would inevitably become malignant, the diagnosis of that lesion would constitute a clear indication for its excision. Theoretically that would not necessarily mean a simple mastectomy. However, the only breast diseases that have been implicated in studies of this problem are diffuse changes that involve both breasts, and parts of each breast, in varying degree. The conglomeration of pathological changes loosely grouped under the heading "chronic cystic mastitis" are the principal bone of contention in the arguments as to what represents a precancerous lesion. Three of the most intensive recent studies (2, 3, 5) of this problem present somewhat divergent points of view in their details, but

are in agreement on the general principle that more mammary cancer is found in women with "chronic cystic mastitis" than in females with normal breasts. Such statistical demonstration of relationship does not necessarily imply cause and effect. The pathological changes of "chronic cystic mastitis" may well be unrelated side-effects of a process which leads to cancer in certain vulnerable areas of epithelium. If the relationship between "chronic cystic mastitis" and cancer is merely one of association rather than that of stages in a continuous process, then the urgency to eradicate such tissue is less. The pathologic change that has been most closely linked to the development of infiltrating carcinoma is that of duct papillomatosis with cytologic atypism, as described by Foote and Stewart. When this lesion is encountered, it may be considered a valid indication for prophylactic simple mastectomy, after careful microscopic definition of the tissue. Such lesions shade so imperceptibly into carcinoma *in situ* and ordinary duct cancer that in many instances the differentiation cannot be made.

The problem is still the definition of a precancerous lesion, probably one component of the "chronic cystic mastitis" complex. The authors are in complete agreement with Campbell that the diagnosis of "chronic cystic mastitis," the presence of a bleeding nipple, or of intraductal papillomas without cellular atypism, do not indicate a prophylactic simple amputation, especially in a young woman.

Before any discussion of the value of simple mastectomy, it would be well to define this operation. It is usually considered to mean a complete unilateral extirpation of the mammary tissue, including the nipple and areola, but without removal of the pectoral muscles, or dissection of the axillary contents. Ordinarily a minimal amount of skin is excised.

Actually, most "simple mastectomies" are only partial mastectomies, as the breast parenchyma extends far more widely than is generally appreciated. Many so-called radical mastectomies do not remove the breast tissue completely, even though the muscles and axillary contents are removed.

Hicken has shown that complete excision of mammary tissue is seldom accomplished in the usual simple mastectomy. His x-ray visualization of the lactiferous ducts has shown that, in 95 per cent of the mammary glands studied, ducts ascended into the axilla, and some even followed the brachial vessels into the axillary apex. Ducts were found to extend down and medially into the epigastric space in 15 per cent of the cases studied. The ducts also were frequently in intimate contact with the overlying skin and were, on occasions, found to cross the midline, pass posterior to the latissimus dorsi muscle border, and also penetrate into the substance of the pectoralis major muscle. This excellent study has made it apparent that the majority of our simple mastectomy operations represent only partial or incomplete mastectomies. This is well illustrated by one of our cases in which a mastectomy was performed for an intracystic papilloma. Five years later the patient had a recurrent intracystic papilloma on the same side (Fig. 1).

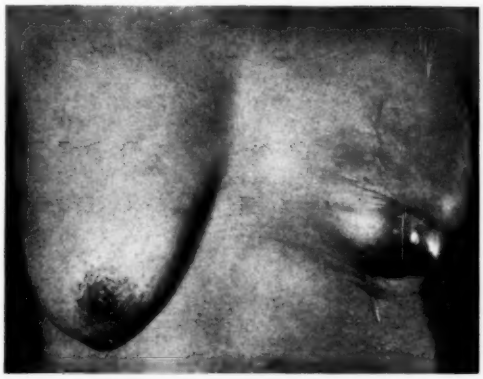

Fig. 1. Photograph of recurrent, benign, intracystic papilloma occurring 5 years after "simple mastectomy" for similar lesion.

DISCUSSION

Review of patients having simple mastectomy shows that the operation is uncommonly indicated and is performed too frequently. It is our belief that this procedure should be performed only on the basis of a carefully defined diagnosis. In other words "simple" amputation of a breast should not be done on suspicion, or just in case of doubt, unless that doubt is communicated to the patient and

she makes the decision, as to acceptance of the risk, or elimination by mastectomy. These doubtful situations may be narrowed down considerably by recognition that the only accepted precancerous breast lesions are those duct changes exhibiting atypical hyperplasia to a degree requiring serious consideration of the diagnosis of cancer. Functional changes to a lesser degree, or in a different direction, can be safely followed without mastectomy by rigid periodic checkups.

Simple mastectomy in other situations would seem to have fairly definite indications. The presence of early cancer in a very poor risk patient is considered to be a worthwhile reason for "simple" mastectomy. Tuberculosis of the breast with extensive and deep involvement is another; recurrent "cystosarcoma phyllodes" or "giant intracanalicular adenomyxoma" with atypical spindle cell stroma is equally an indication for mastectomy. Occasionally fat necrosis involves the entire breast tissue with sinus formation; local excision of such lesions is impracticable, and in fact, impossible. Mastodynia of a very severe degree may rarely indicate removal of a breast. Endocrine therapy can relieve, or ameliorate to a bearable degree, most of these situations. We believe that simple mastectomy has a very definite but limited place in palliative treatment of advanced breast cancer. Bulky, ulcerated masses should be removed, but if the axillary involvement is operable and the patient in adequate physical condition, a radical mastectomy, possibly with skin graft, is preferable. Radiation should always be used in palliative problems.

SUMMARY AND CONCLUSIONS

The operation of simple mastectomy is performed far too frequently for benign breast lesions. The usual operation of this type is inadequate and does not remove completely the breast tissue. Such limited surgery is useful, but not when a diffuse lesion of the breast is being treated, and particularly not when the operation is done for a "precancerous" lesion as prophylaxis against cancer. Such "prophylactic" amputation of a breast should be done only on very well considered biopsy material, which is interpreted as showing diffuse duct epithelial changes of atypical hyperplasia of a marked degree. We consider the indications for simple mastectomy to be as follows:

1. Therapeutic, when a diagnosed disease of the breast is being treated.

a. Palliative for advanced, inoperable breast cancer with a bulky, ulcerating mass.

b. Palliative for cancer in poor risk patients.

c. Sarcoma of the breast.

d. Chronic suppurative infections of the breast, either non specific or tuberculous, which have destroyed much breast tissue.

e. The rare case of uncontrollable and severe mastodynia which does not respond to endocrine therapy and which requires opiates for relief.

f. The rare case of diffuse fat necrosis throughout the breast, with sinus formation.

2. Prophylactic.

a. Multiple or diffuse, and recurrent benign tumors with malignant potentials such as multiple intracystic papillomas, and cystosarcoma phyllodes.

b. Precancerous chronic cystic mastitis, showing diffuse duct changes of advanced atypical epithelial hyperplasia.

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TRANSABDOMINAL GASTRIC VAGOTOMY

A Study of the Anatomy and Surgery of the Vagus Nerves at the Lower Portion of the Esophagus

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A LARGE variety of surgical procedures for the treatment of peptic ulcer have been introduced since Billroth first devised his epoch making operations on the stomach. With the advent of each new operation, fresh impetus has been supplied to a study of the anatomy of the organs and structures involved in the newer techniques. The recent introduction by Dragstedt and his associates (1–5) of complete division of the vagus nerve supply to the stomach as a method of treatment for peptic ulcer has focused the attention of the surgeon and the anatomist alike on the finer anatomy of the vagus nerves and the variations in the distribution of these structures at the lower portion of the esophagus. At the University of Chicago Clinics, approximately 300 of these operations have been performed to the present time. The clinical results have been so satisfactory and the complications so transitory and inconsequential that this method has very largely replaced all other types of surgical treatment for this disease in this Clinic. As experience has accumulated, the necessity for complete division of the vagus supply to the stomach has become more evident. Physiological tests on 170 patients on whom the operation was performed by us have revealed that the vagus section was probably incomplete in 18 cases. In this group, 6 patients have complained of recurrent or persistent ulcer symptoms, and in 2 of these, an undamaged vagus fiber was found at a second operation. Division of this nerve was followed by complete relief. The remaining 164 patients have remained free from all types of ulcer distress on an entirely unrestricted diet and without medication. In general, a complete vagotomy is manifested by a profound decrease in the volume and acidity of the continuous night secretion and a negative gastric secretory response to insulin hypoglycemia and the sham meal. It is a striking fact that the excessive continuous night secretion of gastric juice characteristic of patients with duodenal ulcer may be unaffected by the section of two large vagus trunks if a single small vagus fiber is left undisturbed. Section of this remaining fiber may then produce the profound decrease in gastric secretion characteristic of total vagotomy.

The present paper represents the outcome of a co-operative effort carried on in the department of anatomy at the University of Illinois under the direction of Dr. O. Kampmeier and in the department of surgery at the University of Chicago. In the anatomical laboratory, a careful dissection was made of the vagus nerves along the lower esophagus in 60 cadavers. Careful records and drawings were made of the variations encountered in the distribution and branches of the right and left vagus nerves along the lower 3 inches of the esophagus, and these have been summarized in Figure 1. It is important to note in this drawing that in 81 per cent of cases, the distribution of the anterior and posterior vagus trunks is as illustrated in Figure 1a and Figure 2. Commoner variations are depicted in Figures 1b, 1c, 1d, 1e, 1f, 1g, and 1h.

In the laboratories of the department of surgery, specimens of the esophagus and stom-

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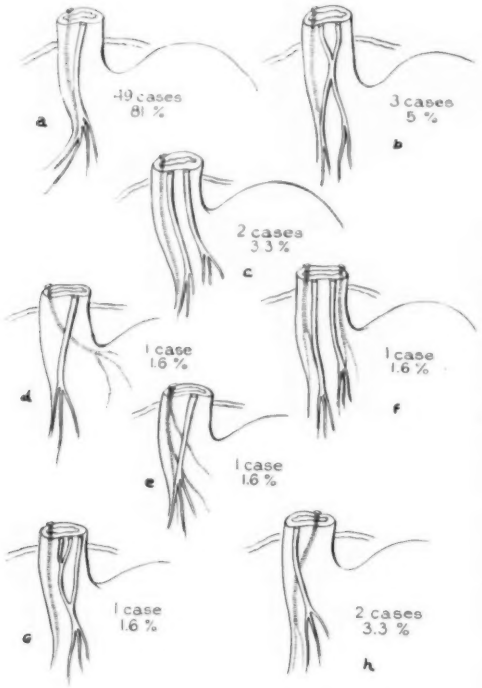

Fig. 1. Sketches showing the distribution of the vagus nerves along the lower portion of the esophagus and upper stomach in 60 human dissection specimens. Note that in 81 per cent of the cases, the distribution is as illustrated in a.

ach were obtained at autopsy from 18 bodies, the vagus nerves carefully dissected, and after the dissection, the specimens were inflated with air and permitted to dry slowly. The vagus nerves were then colored with white ink to make them stand out sharply in the photographs (Figures 3–12). It is probable that a better understanding of the vagus nerve supply to the stomach can be secured from inspection of the drawings and photographs than could be provided by textual description.

The studies referred to above have been correlated with the less exact observations made at the operating table during the course of division of the vagus nerves to the stomach either by the transthoracic or by the transabdominal approach. In the series of 170 patients in which reliable physiological evidence concerning the completeness of the vagus sec-

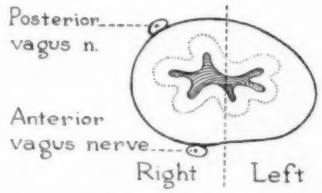

Fig. 2. A drawing of a transverse section of the esophagus just below the diaphragm showing the most frequent position of the posterior and of the anterior vagus nerve. Note that both nerve trunks are on the right of the esophagus.

tion is available, the operation was performed by the transthoracic approach in 61 patients and by the transabdominal route in 109 patients. Analysis of these data indicates that we were just as successful in securing a complete vagotomy by the transabdominal operation as by exposure of the esophagus in the chest. A careful consideration of the technique employed in the transabdominal operation is, however, very necessary because it seems very likely that the abdominal methods described by Stierlin, Schiassi, and others would very rarely, if ever, yield a complete division of the vagus fibers to the stomach. It should be emphasized that in both the transthoracic and in the transabdominal operation, the vagus nerves are divided at a point 2½ to 3 inches above the junction of the esophagus with the stomach. Regardless of the type of approach, the operation is a supradiaphragmatic section of the vagus nerves.

A midline incision is made from the xiphoid cartilage to a point 2 or 3 centimeters below the umbilicus. An exploration of the abdomen is then made with especial care to determine the nature and extent of pathology in the stomach and duodenum. If the ulcer is in the duodenum, it is important to determine the presence or absence of cicatricial obstruction at the pylorus. Helpful information can be secured by palpation or by the passage of the Levine tube, which is present in the stomach through the pyloric sphincter. If cicatricial obstruction at the pylorus is found, the vagus section should be combined with a gastroenterostomy or a gastroduodenostomy. The vagus section is best performed first. While the surgeon makes gentle, downward traction on the left lobe of the liver, his assistant divides

Fig. 3.

Fig. 4.

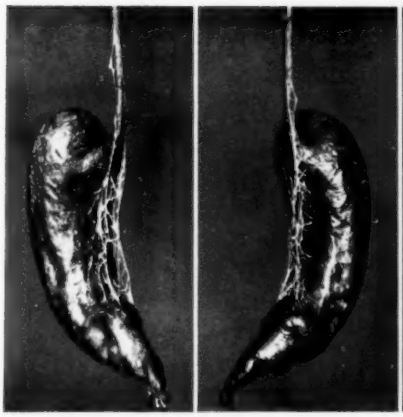

Fig. 5.

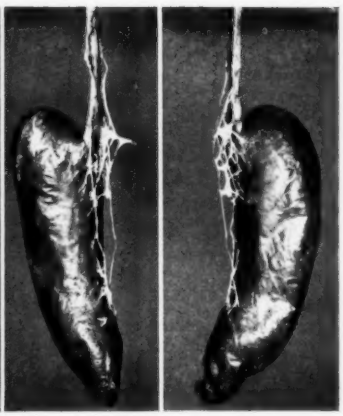

Fig. 6.

Figs. 3–12. Photographs showing the distribution of the vagus nerves to the esophagus and stomach in man. The vagus nerves have been dissected out, colored with white ink, and the stomachs inflated with air before the photographs were taken. Note that both vagus nerves terminate along the lesser curvature of the stomach, that there are frequent anastomosing branches between them, but no true plexus formation.

the triangular ligament with scissors until the lower esophagus is uncovered. The left lobe of the liver is then retracted firmly to the right with a cloth-covered spring retractor. The tube in the stomach facilitates palpation of the lower portion of the esophagus. The peritoneum overlying the esophagus at the margin of the diaphragm is secured with forceps and incised. The scissors is then thrust upward into the mediastinum over the esophagus and the opening enlarged. The index finger is introduced through this opening into the mediastinum, and the esophagus mobilized by careful finger dissection. It is important to exercise great care in this dissection, since at least one case has been reported in which the esophagus has been opened. During mobilization of the esophagus in this procedure, it is important not to dislocate the vagus trunks by inserting the finger between the nerves and the esophageal wall. If care is taken, the nerves as well as the esophagus can be encompassed by the index finger and pulled downward into the abdomen. The vagus trunks are appreciated by palpation as firm, unyielding cords against the more elastic esophageal musculature. The right or posterior trunk is separated from the esophagus with the fingers and pulled around to the left or splenic side of the esophagus. It is usually possible to get

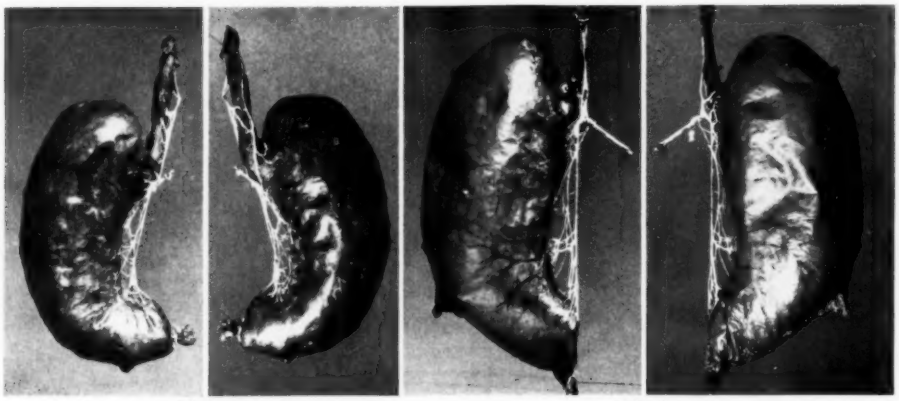

Fig. 7. Fig. 8.

two or three fingers under the nerve trunk in this maneuver, thus exposing from 2½ to 3 inches of the nerve. It is our practice to secure this nerve as high as possible with a hemostatic forceps and apply a ligature of nonabsorbable suture material, either silk or linen, above the hemostat. The nerve is then divided and the distal end pulled downward on the stomach. It is usually possible to excise 2 inches of the trunk for microscopic examination and also as a preventive against subsequent regeneration. The anterior vagus nerve is then separated from the esophagus by a similar maneuver, ligated, and a portion excised. The longitudinal musculature of the esophagus will now be found to relax somewhat, permitting the esophagus to be pulled still farther into the abdominal cavity. This makes possible the careful inspection of the lower 3 inches of the esophagus, and it is wise at this stage to pick off all strands of fascia and possible nerve fibers with a pair of forceps. In rare cases, a branch of the vagus nerve, either anterior or posterior, may be found incorporated in the esophageal musculature or immediately superficial to the mucous membrane. Such branches are readily missed and can be detected only by careful palpation after tension is exerted on the esophagus in several directions. When satisfied that the vagotomy is complete and that hemostasis has been secured, the operator closes the opening into the mediastinum with three or four interrupted catgut sutures. The left lobe of the liver is now replaced, but it is usually unnecessary to suture the triangular ligament. If cicatricial obstruction of the pylorus has been found, a gastroenterostomy or gastroduodenostomy should now be performed.

POSTOPERATIVE MANAGEMENT

The postoperative care of patients upon whom a total gastric vagotomy has been performed is most important. It is probable that most of the motor disturbances in the stomach that have been encountered are due to failure to appreciate this fact. The mammalian stomach, like the heart and the amphibian lung, possesses a true peripheral automatism which makes it possible to display its characteristic motor function in the absence of all nervous connections with the central nervous system, or even if entirely removed from the body. It is well known that strips of stomach or intestine suspended in oxygenated baths of Ringer's solution or Locke's solution will contract rhythmically for many hours and in response to various types of stimulation. While this is true, under normal conditions, the stomach *in situ* is influenced by two sets of extrinsic nerves, the vagi and the sympathetics. These two systems are in constant, but varying, tonic activity. While both motor and inhibitory fibers have been demonstrated in the vagus nerves, it is probable that in man, as in the cat and dog, the predominant effect of the vagus on the motility of the cardia is inhibitory. It is motor or augmentor to the

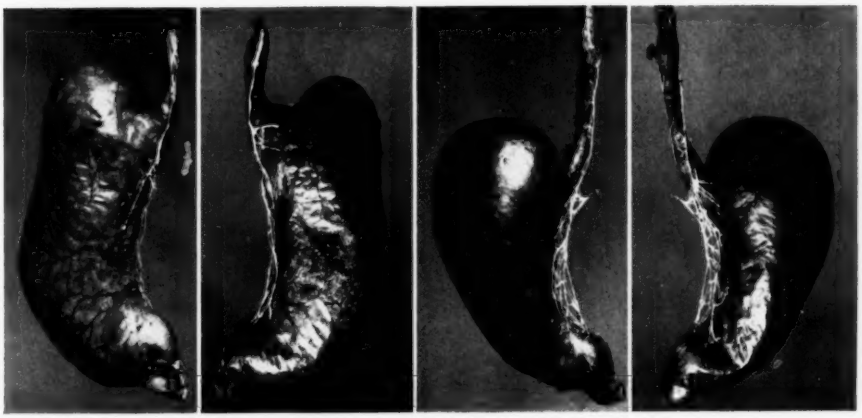

Fig. 9. Fig. 10.

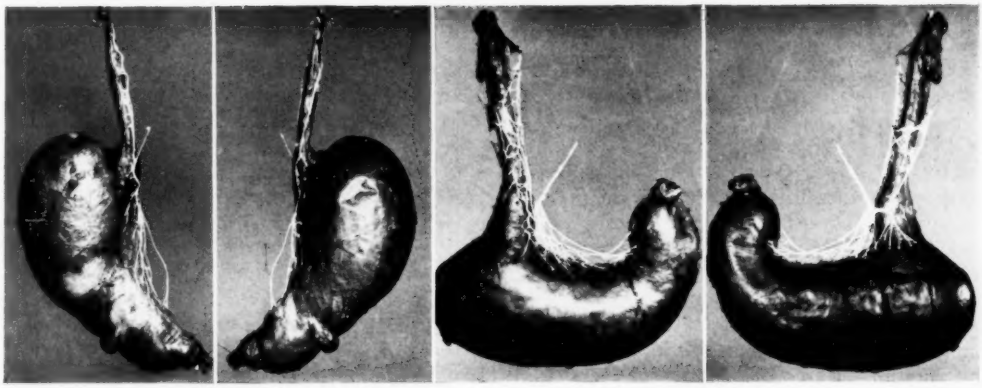

Fig. 11. Fig. 12.

antrum and body of the stomach and inhibitory to the pylorus. In general, the influence of the sympathetic nerves is antagonistic to that of the vagus. When the vagus effect is then suddenly removed, the peripheral motor mechanism of the stomach is subjected only to the activity of the sympathetic nerves and to those humoral influences which come to the stomach by way of the blood stream. If the vagus nerves in the dog are divided high in the chest, a marked increase in the tonic activity of the cardia and pylorus is produced which, in some cases, amounts to a true cardiospasm and pylorospasm. On the other hand, the tonus and motility of the body and antrum of the stomach is markedly reduced. Although we have carefully watched for this complication, we have not yet seen a comparable cardiospasm in man following vagotomy from 2 to 3 inches above the stomach. It is possible, however, that vagotomy at a higher level might produce this complication.

It is difficult to determine the presence of pylorospasm in human patients, and especially when an ulcer is present in the duodenum. Obstruction at the pylorus could be due to the unopposed motor action of the sympathetic nerves, to local spasm or edema, or to actual scar tissue narrowing. It is our impression that a pylorospasm comparable to that seen in many dogs following high vagotomy is not commonly seen in the human patient. The

unopposed inhibitory effect of the sympathetic nerves on the tonus and motility of the body of the stomach, however, makes it easy to produce a marked dilatation and distention of this part of the organ. In the immediate postoperative period, this dilatation and distention are most commonly due to the accumulation of swallowed air and gastric and intestinal secretion. Occasionally, it may be due to the overingestion of food and drink. Overdistention and dilatation of the stomach markedly delay and interfere with the readjustment of the peripheral motor mechanism and may make the postoperative care of these patients very difficult. If this overdistention of the stomach is prevented, a readjustment in the peripheral motor mechanism takes place, so that in a relatively short period of time, the motor function of the stomach resembles that seen in normal individuals. It is probable that the hypermotility, which characterizes many of these patients before vagotomy, is never regained. The mechanism of this readjustment after vagotomy is not known. Presumably, it might be due to a gradual decrease in the tonic influence of the sympathetic nerves or to an increased activity and influence of the local nerve plexus of Auerbach. While a varying length of time is required by different patients for the peripheral readjustment of the gastric motor mechanism, in our experience, the following management has usually been successful.

A Levine tube is introduced through the nose into the stomach from 24 to 48 hours before the operation, and the stomach is decompressed by the Wangensteen apparatus. The tube is left in place for 4 or 5 days following the vagus section, and great care is observed during this period to make sure that the stomach is completely decompressed. A marked reduction in the volume and acidity of the gastric secretion removed from the stomach after operation as compared with the amount secured in a comparable period before is a good index of the completeness of the vagotomy. When the tube is removed on the fourth or fifth day, the patient is permitted to take 30 cubic centimeters of water per hour for the first day. At the end of the day, the stomach is aspirated, and if it is empty, 60 cubic centimeters of water per hour is permitted for the following day. If aspiration reveals that this larger amount has left the stomach, the patient is placed on a clear liquid diet for 2 or 3 days. The patient is instructed to cease eating if he feels distended. If the liquid diet leaves the stomach satisfactorily, semisolid food in small amounts is gradually added. The patient is instructed concerning the alterations in the physiology of the stomach that result from the operation, and his co-operation is sought in preventing overdistention in the immediate postoperative period. Some patients have returned to a full diet within 2 to 3 weeks without ill effects, while others, more cautious, have voluntarily restricted the intake of food for 5 or 6 weeks. If the stomach has not become overdistended in the immediate postoperative period, it is likely that most patients regain normal motor function within 6 months. It is well to bear in mind, however, that a large ulcer crater in the duodenum may produce cicatricial obstruction on healing that was not observed at the time of the operation. While it is true that urecholine in suitable doses increases the motor activity of the vagotomized human stomach, we have not found it necessary or advisable to use this drug in the routine postoperative care of these patients.

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MEDIASTINAL CYSTS AND TUMORS

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OVER 12 years ago George J. Heuer (26, 28) stated "The subject of intrathoracic tumors has already become so large that it is difficult to deal with it in a short paper." What he said then of intrathoracic tumors is now true of mediastinal tumors. However, because of the difficulties attendant on diagnosis of mediastinal tumors and the vital necessity of keeping all tumors in mind in differential diagnosis of individual cases, it is well to publish occasional summaries to view more clearly the whole subject. All too often papers are published on benign intrathoracic or mediastinal neoplasms without emphasizing, as John Alexander (5, 6) does, that "The majority of circumscribed intrathoracic neoplasm arise within the lung (almost all of them being malignant); many of those that arise outside the lung are malignant; and, therefore, the prompt removal of any circumscribed neoplasm which cannot be proved benign is of vital importance."

An adequate classification of mediastinal tumors can be obtained by combining the classifications which were used by Carlson, Laipply, and Heuer (25) in the following manner:

I. Congenital cysts
   1. Epidermoid cysts — Ectoderm
   2. Dermoid cysts — Ectoderm and mesoderm
   3. Teratoma — Ectoderm, entoderm and mesoderm
   4. Pericardial celomic cysts — Mesoderm
   5. Bronchial cysts — Entoderm and mesoderm
   6. Esophageal cyst — Entoderm and mesoderm
   7. Gastroenteric cyst
      a. Gastric — Entoderm and mesoderm
      b. Enteric — Endoderm and mesoderm
   8. Cystic lymphangioma — Mesoderm

II. Acquired cysts
   1. Parasitic cyst, caused by Taenia echinococcus
   2. Neoplastic cyst, due to degeneration of a solid tumor
   3. Cystic hematoma, resulting from degeneration of hematoma

III. Connective tissue tumors
   1. Fibromas
   2. Lipomas
   3. Leiomyomas
   4. Xanthomas
   5. Chondromas
   6. Chondromyxomas
   7. Chondromyxosarcomas

IV. Neurogenic tumors
   1. Neurofibromas
   2. Ganglioneuromas
   3. Neuroblastomas
   4. Neuroepitheliomas

V. Primary tumors of thymus
   1. Benign thymomas
   2. Malignant thymomas
   3. Thymic cysts

VI. Primary tumors of lymph nodes
   1. Lymphosarcomas
   2. Hodgkin's disease
   3. Boeck's sarcoid (?)
   4. Endotheliomas

VII. Primary and secondary sarcomas

VIII. Primary and secondary carcinomas

IX. Intrathoracic goiters

A discussion of the symptomatology of such a large group of tumors is virtually impossible, as the individual cases vary from the asymptomatic (by far the largest group) to expectoration of tumor contents and obstructive symptoms causing death. All of the classical symptoms of chest pathology may be present in individual cases, or, which is more usual, none. The physical examinations, too, are extremely variable, depending on the size, location, consistency, presence or absence of infection, and extent of involvement of adjacent structures. Roentgenograms are an invaluable aid in this field where physical findings are all too frequently minimal or completely absent. Heuer and Andrus in their excellent monograph (27) on "The Surgery of Mediastinal Tumors" repeatedly emphasize that surgery is indicated in all mediastinal tumors, not only for treatment but as the only means of positive diagnosis in most cases.

CONGENITAL CYSTS

Epidermoid cysts, dermoid cysts, and teratomas. The first three types of congenital cysts are grouped as one, when discussing

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Fig. 1.

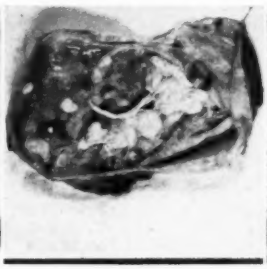

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1. Preoperative roentgenogram. Area of density in right mediastinum.

Fig. 2. Gross specimen.

Fig. 3. Cyst lined by squamous epithelium. Thymic lymphoid tissue in wall.

Fig. 4. Postoperative roentgenogram.

their origin. Two plausible hypotheses have been advanced to explain pathogenesis of these tumors, the monogerminal and the bigerminal. Rusby adequately reviews the evolution of these theories and thinks the monogerminal theory is the more reasonable, that the explanation lies in an abnormality of the third and fourth branchial arches, with the abnormal cells being carried into the thorax by the normal descent of the heart and great vessels. He is careful to state that the problem is not yet solved.

Since the original report by Gordon in 1823 to the present time there have been many reviews of this subject in the literature, notably Hare (1889), Dangschat (1903), Hertzler (1916), Heuer (1926), Hedblom (1933), and Rusby (1944). In 1945 Laipply totaled the cases of epidermoids, dermoids, and teratomas at 245, adding a dermoid of his own.

The importance of these tumors lies in the facts that: (1) They may cause pressure symptoms as they increase in size. (2) They may become secondarily infected. (3) They may rupture into a bronchus, a blood vessel, or the pleura. (4) They may degenerate to malignancy. For these reasons, plus the fact that positive diagnosis is impossible in most cases, all writers agree that surgical excision is the treatment of choice.

The differentiation between epidermoid, dermoid, and teratoma can usually be made grossly if the cyst contents are well defined with adult structures present; particularly in the first two, however, the microscopic picture will frequently cause the gross diagnosis to be changed. Epidermoid is the simplest of the cysts lined by stratified squamous epithelium supported by fibrous tissue, and its contents are desquamated and degenerated epithelial cells. Dermoid cysts are lined by stratified squamous epithelium with added elements in their walls of structures ordinarily arising from skin; sebaceous glands, coil glands, hair and teeth. The teratomas include elements of all three layers so that all structures of the epidermoid or dermoid may be present plus ciliated and cylindrical cell structures of gut or respiratory tract origin; muscle, bone, cartilage, lymphoid tissue, brain and thyroid.

We offer four cases in this group: 1 dermoid and 3 teratomas.

Case 1. J. E. H., 23 year old white male, had a routine chest roentgenogram which demonstrated a mediastinal tumor. Patient was completely asymptomatic. Physical examination was negative except for slight dullness to percussion and diminution of breath sounds in the anterior right chest extending from the right border of cardiac dullness to the nipple line. Laboratory studies were negative. Roentgenograms showed a circumscribed area of density in the anterior right mediastinum. Fluoroscopy showed no evidence of communication with the vascular system. Thoracotomy and removal of a dermoid cyst in the anterior mediastinum was performed November 9, 1945. Patient was returned to the ward in good condition, and postoperative course was uneventful. Pathological examination of the tissue showed a cyst measuring 11 by 10 by 8 centimeters in size from which, on cutting, a large quantity of yellow turbid material escaped under pressure. There were numerous strands of tissue resembling epithelium, but no hair was noted. Cyst wall was lined by a flat layer of squamous epithelium, and clinging to the surface were numerous laminations of desquamated squamous epithelium.

Fig. 5.

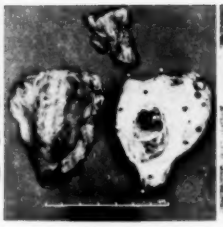

Fig. 6.

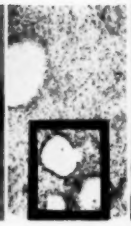

Fig. 7.

Fig. 8.

Fig. 5. Preoperative roentgenogram. Case 3. Tumor of superior mediastinum.
Fig. 6. Gross specimen.
Fig. 7. Microscopic section showing tubular structures.
Fig. 8. Postoperative roentgenogram showing metastases.

Diagnosis: cyst, dermoid, thoracic, mediastinal, right. (Figs. 1 to 4.)

CASE. 2. G. W. A., 20 year old white male, had a routine chest plate which showed an anterior mediastinal tumor. Patient was asymptomatic. Physical examination was negative. Laboratory studies were within normal limits except for the roentgenogram which showed a large mediastinal tumor extending into the right pleural cavity. Fluoroscopy showed no evidence of connection with the vascular system. Exploratory thoracotomy showed a large mediastinal tumor on the right which was removed without difficulty. Patient was returned to the ward in good condition, and postoperative course was uneventful. Pathological report showed a 13 by 9 by 8 centimeter cystic mass, which on cut section showed semitranslucent gelatinous material with about 490 cubic centimeters of brown watery fluid in the center. Microscopic section showed a dermoid ridge containing typical epidermis, sebaceous glands, an occasional hair, and several hair follicles; also, apocrine-type sweat glands. Some smooth muscle was present, and a segment of tissue resembling a small portion of gut. There was a well defined cartilage present suggesting a possibility of an attempt at bronchus formation. There was a small amount of pancreas-like tissue, with a definite island of Langerhans in the center. Diagnosis: cyst, benign, teratoma, mediastinum, right.

CASE 3. A. J. L. This 23 year old white male complained of shortness of breath on exertion 1 year previous to admission to this hospital. Very occasionally he had a mild pain in the anterior left chest at the level of the second, third, and fourth ribs, sharp in nature, and of short duration. Roentgenograms at that time showed a tumor of the superior mediastinum 8.5 by 9.5 by 7.5 centimeters in diameter with sharp distinct borders and of uniform density. Trachea was displaced to the left and anteriorly and was compressed. The tumor did not pulsate, was not connected with the aorta. Bone roentgenograms at that time showed no metastasis in the skull, dorsal spine, lumbar spine, or pelvis. There was a circumscribed area of increased density at the neck of the right femur, but not suggestive of metastasis, probably normal variation in bone density. Two months after onset of his symptoms, he developed malaise, fever, sweats, productive cough with blood-tinged sputum, and the diagnosis of pneumonia. He recovered from these symptoms following sulfathiazole therapy, then he was treated with an unknown amount of deep x-ray radiation and the diagnosis of lymphoma, superior mediastinum, was made. Following this treatment, patient was discharged to return in 6 months for a check-up. On return after a 6 months' period, there was a noticeable enlargement of the tumor mass, and he was transferred to this hospital for further study. On admission to this hospital, his only complaint was exertional dyspnea. He had no cough, sputum, hemoptysis, or weight loss. Physical examination was essentially negative. Laboratory studies were within normal limits except for the roentgenograms of the chest which showed a circumscribed sharply demarcated tumor in the posterior superior mediastinum extending to the right of the midline pushing the esophagus 2 centimeters to the left of the midline. There was no pulsation of the tumor. Mediastinotomy was performed through a necklace incision, the tumor was palpated posterior to the trachea largely to the right. Blunt dissection exposed the tumor, its upper cone-shaped wall was free with no thyroid connection. The tumor was removed intact. It was not attached to any organ, and appeared completely encapsulated. Small cystic areas were seen in the cut surface. Immediate recovery from operation was uneventful. Two weeks following surgery an 8 centimeter mass was felt in the left upper quadrant, medial to spleen. Three weeks postoperatively, both lung fields contained numerous rounded shadows of homogeneous density, 1½ centimeters in size, diagnosed as metastases. X-ray therapy was started immediately, and the patient received a total of 900 roentgens through each of four

Fig. 9.

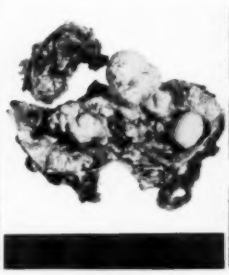

Fig. 10.

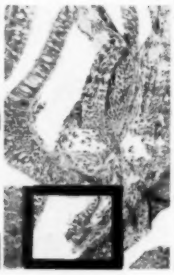

Fig. 11.

Fig. 12.

Fig. 9. Preoperative roentgenogram. Case 4. Left anterior mediastinal tumor.

Fig. 10. Gross specimen.

Fig. 11. Showing ciliated epithelium with goblet cell lining cystic spaces of cystic teratoma.

Fig. 12. First week postoperative roentgenogram.

portals during the next month. His progress was steadily downhill, and he expired 3 months following surgery. Pathological report showed that the tumor appeared to be a solid teratomatous tumor (mixed tumor) of mediastinum. Areas in it were so cellular as to suggest bone carcinoma and sarcoma depending on the area observed and the cell type that had proliferated. Mitosis were occasionally seen. They seemed confined to the connective tissue cell. Diagnosis: teratoma, tumor of the mediastinum, malignant. (Figs. 5 to 8.)

Case 4. J. P. O'M., 32 year old white male, was well until 8 months previous to admission when he noticed a dull ache in the left shoulder which gradually became worse until it kept him awake at night. His symptoms were never severe enough to require hospitalization or examination by a physician. While at a separation center, a routine roentgenogram showed a mass in the left upper mediastinum. Physical examination showed a visible and palpable pulsation, synchronous with systole, in the second left interspace. The mediastinum was widened to percussion in this area. Fluoroscopy showed a nonexpansive, left anterior mediastinal tumor with some plaque-like calcification in the lateral wall. Esophagus was negative. Exploratory thoracotomy showed a large mediastinal teratoma located in the left anterior mediastinum extending upward into the root of the neck. The mass was completely removed; patient returned to the ward in good condition; postoperative course was uneventful. Pathological examination of tissue showed a fragmented cystic structure weighing 133 grams with irregularly sized, round to oval peduculated tissue masses covered with pale squamous epithelium from which numerous pale hairs protruded. The cyst wall was flattened and covered with sebaceous material. Grossly no bone, teeth, or definitely teratomatous tissues were encountered. Microscopic section showed the lining of the cavity composed of a layer of squamous epithelium varying slightly in width. There were acini of mucous glands closely resembling those seen in the bronchus. In other areas, tubules lined by tall columnar ciliated cells were seen with occasional goblet cells in the wall. There were bundles of smooth muscles associated with these tubules and occasional glandular structures. One small spicule of calcified material was seen which may have been bone. Diagnosis: teratoma, cystic, mediastinal, benign; dermoid features predominating. (Figs. 9 to 12.)

Pericardial celomic cysts. The thin-walled cysts of the mediastinum have caused some discussion since Churchill described the findings at operation in Cabot's Case 23492. He did not mention the term "spring water" cysts at that time, but the name is now attributed to him. Mallory gave the pathological report on the same case, describing the cyst lining as "mesothelium" with the cells "ordinarily so thin that they can hardly be distinguished from endothelium, but they occasionally thicken up to a cuboidal type of cell that looks quite like epithelium".

Lambert seems to have adequately explained the origin of these cysts in his theory of failure of one of the primitive pericardial lacunae to merge with the others, thereby forming a cyst. If we can combine the "spring water" cysts and the "pericardial celomic" cysts reported (Dufour, H. and Nourret, 1929; Pickhardt, O. C. 1934; Churchill, E. D. 1937; Lambert, A. V. S. 1940; Greenfield, I. *et al.* 1943) there are only 7 that meet the requirements of (1) a thin-walled cyst, (2) clear fluid, (3) a lining membrane of endothelium or mesothelium that may "look quite like epithelium." Seven seems entirely too few cases to be reported, as we have 8 that meet the

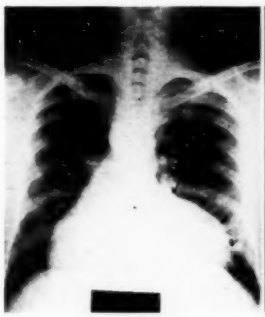

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 13. Preoperative roentgenogram. Case 12. Soft tissue mass in anterior right thorax.

Fig. 14. Preoperative bronchogram.

Fig. 15. Gross specimen.

Fig. 16. Showing simple fibrous wall with surrounding fat. Epithelium is denuded.

above criteria. Possibly when the present confusion regarbing classification is settled, more cases will be reported.

CASE 5. I. H. B., 30 year old white male, noted a sensation of pressure and fullness in the epigastric region 2 months previous to admission. There was very slight dyspnea on exertion, otherwise asymptomatic. Physical examination was negative. Laboratory studies were negative except for the chest roentgenogram which showed a well circumscribed opacity at the cardiophrenic angle on the right. Exploratory thoracotomy showed a cystic lesion attached by a pedicle to the pericardial phrenic angle, and it was easily removed. Recovery from operation was uneventful. Pathological report showed a cystic lesion measuring 8.5 by 5.5 by 7 centimeters in diameter with absolutely clear fluid and a very thin wall so that newsprint could be read through the specimen. Microscopic section showed the inner surface lined with flat epithelium and an occasional area composed of a few cuboidal cells. The cells rested on a hyaline membrane varying slightly in thickness, and appearing to be composed of connective tissue. No squamous epithelial structures were noted in the wall, and there was no ciliated epithelium. Diagnosis: cyst, simple, pericardial (celomic) mediastinum, right.

CASE 6. T. C. K., a 45 year old white male, had complained of pain in the left chest, dyspnea, malaise, and productive cough of 4 months' duration. There was a weight loss of 12 pounds in the past 2 months. Physical examination was essentially negative. Laboratory tests were negative except for roentgenogram of the chest which showed a well circumscribed dense mass in the left lower lung field. Exploratory thoracotomy showed a large cyst occupying the angle between the diaphragm and the pericardium, with a broad attachment to the pericardium. The cyst was dissected free and removed by blunt and sharp dissection. Recovery from the operation was uneventful. Pathological report showed a cyst with no epithelial lining. The walls were composed of acellular fibrous, lamellae with some hyalinization, and in one section granular calcium disposition in a small area of degeneration of fibrous tissue. A serous layer covered the outer surface, apparently pleura. Diagnosis: cyst, serous, unilateral, intrathoracic, left.

CASE 7. O. F. K., a 32 year old white male, had a routine chest plate which showed an opacity in the medial and anterior portion of the right chest contiguous with the diaphragm. History and physical examination were completely negative. Laboratory tests were completely negative, except for the roentgenogram which showed a well demarcated, elliptical, soft tissue mass in the right cardiophrenic area anteriorly. Gastrointestinal series was negative. Thoracotomy showed a clear, thin-walled cyst containing approximately 100 cubic centimeters of clear fluid, freely movable, and attached by a pedicle to the cardiophrenic angle. The cyst was removed, the patient returned to the ward in good condition, and recovery was uneventful. Pathological report showed the cyst containing crystal clear fluid, and newsprint was easily read through the cyst. Microscopic section of the cyst wall was thin and composed of parallel hyaline connective tissue fibers. Lining cells were flattened and no evidence of cilia was seen. Diagnosis: cyst, spring-water, (celomic), mediastinum, right.

CASE 8. R. S. S. This 27 year old white male had a routine roentgenogram of the chest which showed evidence of mediastinal tumor. History was completely negative. Physical examination showed a slight limitation of motion of the right chest with a flat percussion note in the lateral aspect of the right base. Breath sounds were diminished in this area, and tactile fremitus was decreased. The rest of the physical examination was normal. Laboratory examinations were within normal limits, except for the roentgenogram which showed a well circumscribed density between the right middle and lower lobes. These findings were suggestive of a benign, cystic,

Fig. 17.

Fig. 18.

Fig. 19.

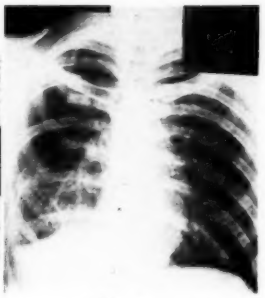

Fig. 20.

Fig. 17. Preoperative roentgenogram. Case 14.
Fig. 18. Opened gross specimen.
Fig. 19. Showing ciliated columnar epithelium.
Fig. 20. Postoperative roentgenogram.

tumor, thought to be attached to the diaphragm or the pericardium. Thoracotomy showed a cyst attached to the cardiophrenic angle by a 2 inch pedicle. The cyst was easily removed. The thorax was closed. Patient returned to the ward in good condition. Recovery was uneventful. Pathological report showed a clear cyst about 8 centimeters in diameter with a thin wall composed of connective tissue with flat epithelium without cilia lining the cyst. Diagnosis: cyst, pericardial, (celomic), mediastinum, right.

Case 9. R. R. DiF. This 31 year old white male complained of vague pains in the epigastrium and upper left quadrant of the abdomen when he ate meat or became nervous. The pains were more severe when the patient was lying down. Duration of symptoms was unknown. Physical examination was negative except for decreased excursion of the left diaphragm which seemed high and immobile. Laboratory examinations were within normal limits with the exception of roentgenograms which revealed an abnormal mass in the left chest which was thought to be a diaphragmatic hernia. Diagnostic studies ruled out a diaphragmatic hernia, and the mass was thought to be primary in the left thorax. Thoracotomy was performed, and a cyst was removed. Pathological report showed a roughly pyramidal cyst measuring 11 by 10 by 7 centimeters with a clear thin wall. Approximately 250 cubic centimeters of thin crystal-colored fluid was evacuated from the cyst. Sections of the cyst wall showed the wall to be composed of laminated connective tissue, the lining of ciliated epithelium. The impression of the pathologist was that this was a mediastinal cyst which has been designated under numerous terms such as cystic lymphangioma, cystic hygroma, ciliated epithelial cyst, or "spring-water" cyst of Churchill. Pathological diagnosis: cyst, mediastinal, probably "spring-water."

Case 10. P. B. This 29 year old colored male was completely asymptomatic but was told he had a chest tumor following a routine roentgenogram. Physical examination was essentially negative. Routine laboratory examinations were within normal limits. Roentgenogram of the chest showed an opaque triangular density in the region of the middle lobe on the right. *Impressions:* Pericardial cyst. Bronchoscopy showed no evidence of endobronchial pathology. On September 5, 1946 right thoracotomy showed a pericardial cysts attached to the anterior cardiophrenic angle, this was easily removed intact. Postoperative course was entirely uneventful. Patient was returned to full duty. Pathological examination showed a pear-shaped fluid-filled cyst weighing 210 grams containing 180 cubic centimeters of crystal clear watery fluid, specific gravity 1.009. Cyst measured 4 by 6 by 7½ centimeters. Microscopic section showed the wall of the cyst formed by compact fibrous tissue. In places there was an outer layer of adult fat which appeared to replace most of the thickness of the fibrous wall; there was some loose scattering of lymphoid cells usually in the fat near a junction with the fibrous wall, and occasional small, flattened-out collections of lymphocytes. No definite Hassell's corpuscles were seen in such areas. A single layer of flattened cells lines the cystic spaces; occasionally these cells seemed thicker, oval; no cartilage was seen in the walls. Diagnosis: pericardial cyst, celomic type.

Case 11. R. F. A. This 32 year old white male was completely asymptomatic. Routine roentgenogram demonstrated a tumor in the right lower chest just above the diaphragm. On admission to this hospital examination revealed decrease of the breath sounds over the right lung field, more noticeable anteriorly; there was very slight dullness of the right lung field in this region; routine laboratory examinations were within normal limits; roentgenogram of the chest revealed a fairly well circumscribed density in the right supradiaphragmatic region in the cardiophrenic angle appearing to be contiguous to the diaphragm. Thoracotomy with removal of the pericardial cysts was performed and recovery was uneventful. Pathological report showed a 10½ by 9½ by 6½ centimeters transparent cyst filled with 200 cubic centimeters of clear watery fluid having a specific gravity of 1.007; microscopic section showed the walls of the cyst to be fibrous, loosely arranged

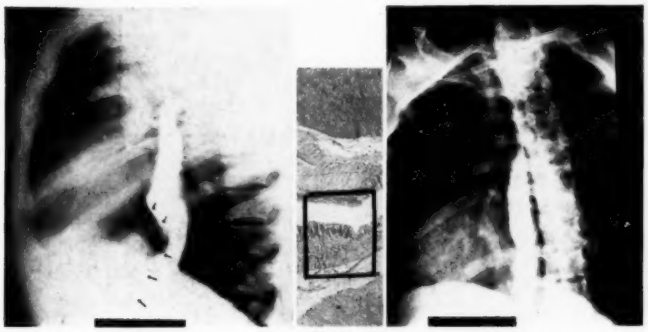

Fig. 21. Fig. 22 Fig. 23.

Fig. 21. Preoperative esophagram. Case 18.
Fig. 22. Showing ciliated columnar epithelium.
Fig. 23. Postoperative esophagram.

and relatively acellular; the inner surface of the wall was lined by a single layer of slightly flattened cuboidal cells having dark staining oval nuclei. Diagnosis: Pericardial cyst, celomic.

CASE 12. E. L. A. This 34 year old white male was completely asymptomatic but a routine roentgenogram revealed a mass in the left lower lung field. On admission physical examination was negative except for examination of the chest which revealed dullness at the right base anteriorally up to the third rib; tactile fremitus was absent at the right base; breath sounds were normal except for this area where they were diminished to absent; roentgenogram of the chest revealed an elliptical soft tissue mass in the anterior right thorax probably adherent to the pericardium and to the medial portion of the diaphragm. Routine laboratory studies were within normal limits; bronchoscopy was negative; bronchograms showed the filling defect apparently external to the pulmonary parenchyma. Exploratory thoracotomy revealed a large pericardial cyst which was easily removed. Recovery from surgery was uneventful. Pathological report showed a 12.5 by 11 by 6 centimeter cyst containing about 300 cubic centimeters of clear, colorless fluid; wall was paper-thin; the cyst was unilocular with several paper-thin, low, baffle-like ridges which could be seen as white fibrous bands through the outer surface. Microscopic showed no epithelial lining although occasional flat cells were seen as if the cysts had been lined by endothelium-like membrane; the wall was composed of acellular strands of connective tissue with fat present in half of the wall close to its original attachment to the mediastinum; a few small collections of lymphocytes were scattered in the wall; the outer surface was covered by a very thin fibrous membrane suggesting mediastinal pleura. Diagnosis: mediastinal cyst (pericardial, celomic, congenital). (Figs. 13 to 16.)

Bronchial cysts of the mediastinum. These congenital cysts of the mediastinum are characterized by ciliated columnar epithelium in their lining membranes. They are of entodermal and mesodermal origin and are generally supposed to arise from the pinching off of a bit of the foregut or tracheal bud which is carried into the mediastinum by the lungs. Cartilage and smooth muscle bundles are frequently present in their walls, and the characteristic cellular lining is frequently destroyed by the pressure of the contained fluid, making diagnosis difficult in some cases unless many microscopic sections are taken to find characteristic epithelium in an untouched recess of the cyst. Treatment is complete excision if possible, but Adams and Thornton (1943) reported good results in 2 cases following partial excision with destruction of the remaining lining mucosa. Laipply (1945) summarized the literature and, with a case of his own, reported a total of 35 cases.

We have 5 bronchial cysts of the mediastinum.

CASE 13. R. E. D. This 25 year old white male had a routine chest roentgenogram which showed a mediastinal tumor. Patient was completely asymptomatic. Physical examination was negative. Laboratory studies were within normal limits except roentgenograms of the chest which showed a large mediastinal mass on the right. Esophagram showed displacement of esophagus to the left by the posterior mediastinal mass. On thoracotomy, a large cystic tumor of the posterior mediastinum was found that lay posterior to the base of the heart, and anterior to the esophagus. The cyst was evacuated, and the entire cyst wall was removed from the mediastinum *in toto*. Before it was opened, the cyst

Fig. 24.

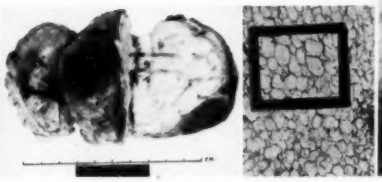

Fig. 25. Fig. 26.

Fig. 27.

Fig. 24. Preoperative roentgenogram. Case 21.
Fig. 25. Opened gross specimen showing fatty lobules.
Fig. 26. Microscopic section showing fat cells.
Fig. 27. Postoperative roentgenogram.

measured approximately 15 centimeters in length, and 8 centimeters in its greatest diameter. Postoperative course was uneventful. Pathological report showed one section of the cyst wall lined by ciliated columnar epithelium typical of that seen in the respiratory tract. The back of the wall was composed of a plate of hyaline cartilage and interposed between it and the respiratory epithelium were flattened mucous glands. Diagnosis: cyst, ciliated, congenital, bronchogenic type, mediastinum.

Case 14. C. L. S. This 24 year old white male noted chest pain and cough productive of large amounts of sputum 5 months previous to admission. One month after onset, a chest roentgenogram revealed a large opacity in the lower lobe of the left lung. Diagnosis at that time was empyema with a bronchopleural fistula, left. Treatment was conservative during the first 5 months of his illness. On admission to this hospital, patient had been coughing up large amounts of mucopurulent sputum during the previous 5 months, with occasional episodes of moderate fever with temperatures running to 101 degrees. He had an indefinite pain in his left chest, transitory in type, never severe. Physical examination was essentially negative except for moderate weight loss, dullness to percussion, and absent breath sounds over the left base, both anteriorly and posteriorly. A thoracotomy with drainage of a large abscess cavity in the lower portion of the left thorax was performed. A biopsy of the abscessed wall at that time showed a cyst lined with respiratory epithelium, citiated. It was felt at the time that the patient had an intrapulmonary, bronchogenic cyst, and he was treated conservatively for 3 months. At the end of that time an exploratory thoracotomy was performed and it was found that the cyst was extrapleural, and originating in the mediastinum. It was dissected free from the left lower lobe and the diaphragm, and amputated from its medial attachments in the mediastinum. The excised specimen, collapsed, measured approximately 10½ centimeters in diameter. Recovery was uneventful, and the left lung completely expanded. (Figs. 17 to 20.)

Case 15. E. F. This 25 year old colored male was asymptomatic. On routine chest roentgenogram, a mediastinal tumor was discovered. Physical examination was negative except for an area of dullness to percussion over the right anterior thorax extending about 8 centimeters from the midsternal line in the 5th intercostal space. Roentgenogram of the chest revealed a right mediastinal tumor mass located between the spine and the heart, displacing the esophagus to the left. The carina was somewhat widened. Exploratory thoracotomy showed a large cystic mass about 8 by 8 by 10 centimeters in size lying behind the bifurcation of the trachea, and anterior to the esophagus. The contents as evacuated, and a cystic sac excised *in toto*. Recovery from surgery was uneventful. Pathological report showed the cyst wall to be composed of partially desquamated layer of ciliated epithelium. The wall contained bundles of smooth muscle which were hypertrophied in some areas, and in other areas the subepithelial tissues were composed of diffuse sheets of hyaline material. Diagnosis: cyst, bronchogenic, ciliated, mediastinum.

Case 16. A. H. B. This 31 year old white male was well until 2 months previous to admission when he had bilateral infectious parotitis complicated by pneumonia. The pneumonia responded well to penicillin therapy, but after recovery from the acute symptoms a large circumscribed intrathoracic tumor was discovered on the roentgenogram examination. On admission to this hospital, he was completely asymptomatic. Physical examination was negative. Laboratory studies were within normal limits with the exception of the roentgenograms of the chest which showed a large tumor mass in the base of the left lung, the heart shadow overlying most of it. It was located in the posterior portion of the left chest extending over to the posterior mediastinum. There had been no change in size since the previous film taken 2 months before admission. Thoracotomy showed a large cystic mass at the base of the left lung seeming to originate in the posterior mediastinum below the hilum of the left lung. The cyst was

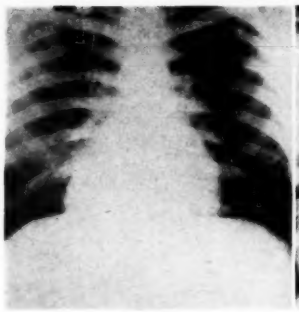

Fig. 28.

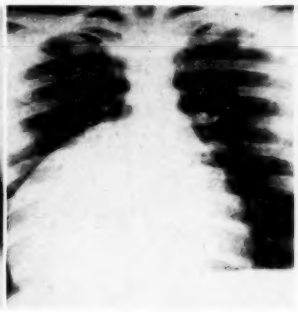

Fig. 29.

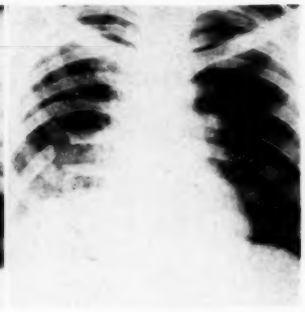

Fig. 31.

Fig. 28. Roentgenogram 2 years before first thoracotomy. Case 22.
Fig. 29. Preoperative roentgenogram, first thoracotomy.
Fig. 30. Gross specimen, first thoracotomy.
Fig. 31. Postoperative roentgenogram, first thoracotomy.

Fig. 30.

markedly adherent to the left lung, and to the left diaphragm. By blunt and sharp dissection, the cyst was removed *in toto*. The thorax was closed and the patient returned to the ward in good condition. Postoperative course was uneventful with the exception of a transient atelectasis which was treated by bronchoscopy on the second postoperative day. Pathological report showed a large cyst approximately 12 centimeters in diameter with a shaggy external surface caused by numerous fibrous adhesions. The cyst was filled with a yellowish, clear fluid, and sections through the wall showed plates of hyaline cartilage and the cyst lined with respiratory epithelium, ciliated. Diagnosis: cyst, bronchogenic, ciliated, mediastinum.

CASE 17. B. I. J. This 22 year old white male had mild intermittent chest pain of 6 years' duration. Roentgenograms taken during the 6 year period were reported alternately as showing "tumor in the chest" and "negative." In 1943 he was rejected by the Army, but in 1944 was admitted to the Army. He completed basic training and served on combat duty 8 months in the European Theater. At the termination of this time he complained of chest pains; however, roentgenograms were read as negative. During a routine chest examination, while undergoing separation, roentgenograms were interpreted as showing neoplasm upper mediastinum, nonmalignant. On admission to Fitzsimons General Hospital physical examination was essentially negative except for soft râles in the right upper chest anteriorly. No evidence of cavitation or consolidation was found on physical examination. Roentgenograms showed a sharply circumscribed tumor mass in the right superior mediastinum with minimal fibrosis at the left apex. Routine laboratory studies were within normal limits. Bronchoscopy was negative. On May 22, 1946 thoracotomy revealed that a mediastinal bronchogenic cyst which was easily removed. Recovery from surgery was uneventful. Pathological report showed a cyst measuring 3.5 by 2.8 by 2.3 centimeters containing very thick jelly-like mucus; lining was irregular, greyish, with scattered small, milk-white, hilanized "bosses." A circular ridge extended from the first ridge to one pole. These ridges were rubbery firm and felt as if they might contain small cartilaginous plates. Microscopic examination showed an outer zone of loose, fibrous tissue with blood vessels and occasional nerves where the cyst was embedded; elsewhere the outer surface was covered by thin mediastinal pleura. Cyst wall within was composed of dense, compact, hyalinized, fibrous tissue covered by a thin flattened epithelium; thick portions of the wall consisted of thick bundles of smooth muscle cells with a few mucus glands and ducts between the muscle layers; lining epithelium in these areas was ciliated pseudostratified cylindrical epithelium. In one area the epithelium was lost and here the cells of underlying stroma showed xanthomatous degeneration. Small collections of lymphocytes are scattered through the wall and in the midzone usually around the engorged capillaries. Diagnosis: bronchogenic cyst, congenital.

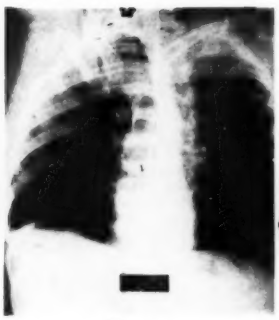

Fig. 32.

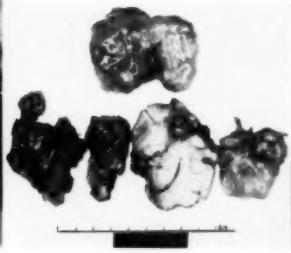

Fig. 33.

Fig. 34.

Fig. 35.

Fig. 32. Recurrence of tumor, 2 years after first thoracotomy. Case 22.

Fig. 33. Gross specimen removed at bilateral thoracotomies.

Fig. 34. Shows myxomatous type stoma and hemorrhage into loose fibrovascular tissue enclosing tumor.

Fig. 35. Postoperative roentgenogram after bilateral thoracotomy.

Esophageal cysts and gastroenteric cysts. These cysts are discussed under one heading because of their similar embryonic origin. Olken, in his excellent review in 1944, summarized three possible explanations for these cysts: (1) pinching off a bud or diverticulum of the embryonic foregut; (2) an intrathoracic remnant of the omphalomesenteric duct; and (3) an embryonic diverticulum or epithelial remnant capable of producing intestinal or gastric mucosa.

Esophageal cysts would be expected to have a stratified squamous epithelium lining. However, since esophageal cysts are remnants of the embryonic esophagus, which has ciliated epithelium, it is reasonable to assume that the cysts could maintain the primitive lining instead of assuming the lining found in the developed esophagus. The possibility that these cysts, in close association with the esophagus, are of bronchial origin cannot be ignored, because at the time of separation of the lung buds from the primitive esophagus, the pinching off of an outbud could occur and become engulfed in the growing esophagus. Therefore, the gross location of these cysts will have to determine their origin; those included within the muscularis of the esophagus can be called esophageal cysts; those located in the rest of the mediastinum or lung can be of bronchial origin. Frequently, in bronchiogenic cysts, cartilage is found in the cyst wall. We present one case in this group, that of a ciliated pseudostratified columnar epithelium-line cyst that was located between the mucosa and the muscularis of the esophagus.

Case 18. A. J. P., a 22 year old white male, had complained of "water-brash" and regurgitation of food of 6 years' duration. While in combat he fainted and roentgenograms showed a pressure defect in the esophagus. The patient was returned to the zone of the interior where roentgenograms confirmed a single pressure defect in the lower third of the esophagus. Thoracotomy showed an esophageal cyst located between the mucosa and the muscular layers. The cyst was enucleated without entering the lumen of the esophagus. It contained fluid. Pathological report showed a cyst with ciliated epithelial lining. Diagnosis: ciliated cyst, esophageal, congenital. (Figs. 21–23.)

Gastroenteric cysts are characterized by the resemblance to gastric and intestinal structures. They are rare, with only 19 cases found by Olken, including 1 of his own, 5 more reported by Ladd and Scott, and 1 by Laipply. All but 3 were in children under 2 years of age. Ladd and Scott had recovery in 3 cases following marsupialization of the cyst and subsequent destruction of its mucosal lining.

Cystic lymphangiomas. These tumors are also called "cystic hygromas." They are extremely rare in the mediastinum. Sanes and associates were able to collect 8 cases from American and foreign literature, including a case of their own. Cystic lymphangiomas are characterized by multiloculated cysts containing fluid with an endothelial lining and smooth muscle and lymphocytes in the walls.

Fig. 36.

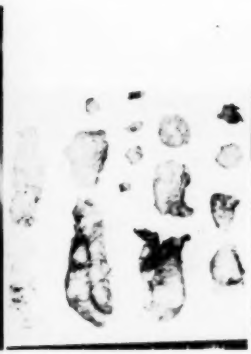

Fig. 37.

Fig. 38.

Fig. 39.

Fig. 36. Preoperative esophagram showing multiple filling defects. Case 23.

Fig. 37. Leiomyomas removed at mediastinotomy.

Fig. 38. Photomicrograph showing interlacing bundles of smooth muscle.

Fig. 39. Postoperative esophagram.

ACQUIRED CYSTS

This group of cysts is mentioned mainly to be kept in mind in differential diagnosis. Echinococcus cysts of the mediastinum are extremely rare compared to the same type of cyst of the lung. Neoplastic cysts are due to degeneration of a solid tumor and any solid tumor in this classification may show these characteristics, more usually the highly malignant types. Hemothorax, other than traumatic, can come from rupture of an aneurysm, degeneration of a neoplasm, or spontaneous hemopneumothorax. In unusual cases they may simulate mediastinal tumors.

CONNECTIVE TISSUE TUMORS

Fibromas. In 1941 Blades reported 32 cases of intrathoracic fibromas in the world literature, indicating the rarity of the lesion. Of these cases, 18 died of pressure symptoms, unoperated upon, and of the 14 cases in which operation was done all lived except one. Clagett and Hausmann (14) successfully removed a 10.9 pound fibroma which they claimed to be the largest intrathoracic tumor ever removed surgically with survival and complete recovery of the patient. Of the 18 cases collected by Heuer and Andrus (28) in 1933, only 5, below the age of 40, had symptoms suggesting that these tumors are "silent" for years before symptoms occur.

Lipomas. Most of the intrathoracic lipomas originate in the mediastinum, as evidenced by Heuer's report (26) in 1933 on 29 cases—25 occupied the mediastinum and 4 were subpleural. They may attain giant size and cause death from pressure symptoms. In Heuer's case, the tumor filled the entire left hemithorax with displacement of heart and mediastinal contents far to the right. McCorkle and associates collected 34 cases in 1940, and of these only 12 were successfully excised. Watson and Urban, and Wiper and Miller each have added successful cases (undoubtedly there are more). We have 3 cases of successful extirpation of a mediastinal lipoma.

CASE 19. R. R. D., a 37 year old white male, had a routine chest roentgenogram which showed a mediastinal mass. History and physical examination were completely negative. Laboratory studies were negative with the exception of roentgenograms of the chest which showed an ovoid tumor mass anteriorly in the right cardiophrenic angle, considered to be possibly a dermoid or substernal diaphragmatic hernia. A gastrointestinal series showed a herniation of the stomach or bowel through the diaphragm. Thoracotomy showed a fatty tumor mass approximately 5 centimeters in diameter located in the cardiophrenic angle on the right. This was easily removed. Patient returned to the ward in good condition, and recovery was uneventful. Pathological report showed a lobulated adipose mass. No noteworthy pathology was seen.

CASE 20. R. L. H., a 30 year old white male, had a mediastinal mass which was seen on routine roentgenogram of the chest. History and physical examination were completely negative. Laboratory studies were negative with the exception of roent-

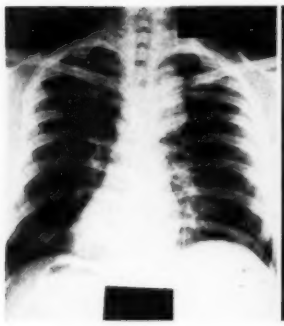

Fig. 40.

Fig. 41.

Fig. 42.

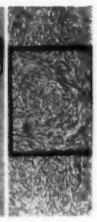

Fig. 43.

Fig. 40. Preoperative roentgenogram, posterioanterior. Case 27.

Fig. 41. Preoperative roentgenogram, lateral.

Fig. 42. Gross specimen.

Fig. 43. Showing interlacing bundles of nerve tissue without palisading.

genograms which showed a mass to the right of the cardiac shadow in the cardiophrenic angle which appeared to be a pericardial cyst. Thoracotomy was performed and the mass was easily removed. Recovery was uneventful. Pathological report showed an irregular oval mass 6 by 5 by 3 centimeters enclosed in a transparent fibrous capsule. Microscopic section showed uniform picture of adult fat cells with fine, widely spaced, fibrous strands outlining indefinite lobules. Diagnosis: lipoma, adult-sized type, mediastinum.

CASE 21. T. H. P. This 44 year old white male was admitted to the hospital complaining of symptoms referable to an indirect inguinal hernia. On routine roentgenograms of the chest, a mediastinal tumor was discovered. History of any chest complaints was completely negative. Physical examination was essentially negative. Laboratory studies were within normal limits with the exception of the chest roentgenogram which showed a rounded shadow sharply circumscribed inferiorly and laterally seen in the right chest suggesting a cyst. The shadow lay posteriorly. Lung markings traversed the area anterior to the mass. The tumor was not so dense as to obliterate the rib markings. Fluoroscopy showed no connection to the cardiovascular elements although the medial attachment of the tumor could not be rotated away from the hilar or mediastinal shadows. There was no pulsation in the tumor. Exploratory thoracotomy through a right Sauerbruch thoracoplastic incision showed a large circumscribed fatty tumor mass. This was removed, the chest closed, and recovery from surgery was uneventful. Pathological report showed an oval, flabby, indurated, yellow fat tumor weighing 225 grams, measuring 11 by 8.5 by 6.5 centimeters in diameter. Microscopic section showed the tumor to be composed for the most part of adult fat cells, but in some areas the appearance was more cellular with an increased number of spindle cells and fibrocytes, and with fat cells that appeared partially collapsed and slightly opaque. No mitoses were seen. Diagnosis: lipoma, mediastinal, growing into right pleura, benign. (Figs. 24–27.)

The mixed types of fatty tumors would come under this heading, such as the fibrolipomas and fibrolipomyxomas. We have one case of fibrolipomyxoma that was operated upon in 1942 but had recurrence bilaterally in 1944. In a two stage procedure, operating on both sides, the tumor was apparently removed.

CASE 22. D. E. G. This 28 year old colored male was first operated upon by Dr. Thomas J. Kinsella, of Minneapolis. He had a mediastinal tumor known for 18 months which measured 21 by 16 by 16 centimeters at the time of operation. The tumor was removed from the right posterior chest and mediastinum and the gross specimen appeared to be well encapsulated but Dr. Kinsella felt that recurrence probably would occur. The pathological diagnosis was benign, degenerating fibroma. Two and one-half years following his first operation, he was admitted to this hospital complaining only of epigastric distress which was consistent with the diagnosis of duodenal ulcer. During his routine studies a chest plate was taken which showed multiple, small round tumor masses in the cardiophrenic angles, bilateral. Thoracotomy was performed on the right, and multiple tumor masses were removed from along the sympathetic chain on the right—the largest mass measuring 10 by 6 centimeters in diameter. One of the masses was almost gelatinous in character, and the operator felt that it was not removed entirely. Two and one-half months after the first operation at this hospital, thoracotomy on the left was performed and four distinct tumor masses were removed from the mediastinum in the region of the sympathetic chain and ganglia. Three nerves passed into the tumor masses. Grossly, it was felt, that these masses had their origin in nerve tissue. Recovery from both operations was uneventful except for mild

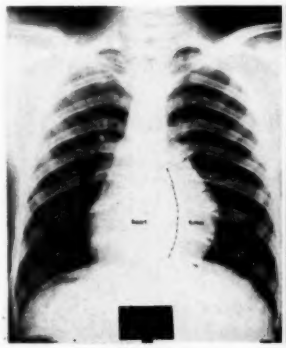

Fig. 44.

Fig. 45.

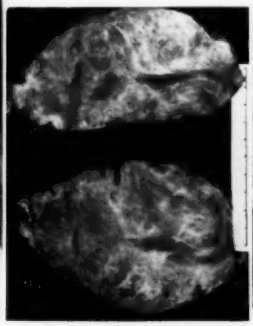

Fig. 46.

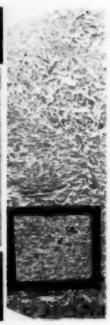

Fig. 47.

Fig. 44. Preoperative roentgenogram, posteroanterior.
Fig. 45. Preoperative roentgenogram, lateral. Case 29.
Fig. 46. Gross specimen, encapsulated ganglioneuroma.
Fig. 47. Showing neurofibrils surrounding ganglion cells.

atelectasis which developed on the second postoperative day following the second operation, and which was treated by bronchoscopic aspiration. Check-up plates taken a month postoperatively showed no evidence of tumor masses remaining in the mediastinum. Patient was advised that he would have probable recurrence and should have frequent x-ray examinations of his chest in the future. Pathological report on all tumor masses was identical. Microscopic sections showed adipose tissue with irregular walls, many of the cell processes appeared to be going on into a myxomatous type of degeneration, and the cells were stellate with hypochromatic nuclei and interlacing cytoplasmic fibrils. No mytotic figures were seen, nor were there sheets of cells. At the periphery of one section, the spindle cells and occasional stellate cells were more numerous, appearing to form a capsule. Impression: Tumors appeared to be benign and encapsulated, and apparently were myxomatous degeneration of lipoid tissue. Diagnosis: myxolipoma, benign. (*Note*: Dr. Thomas J. Kinsella has reviewed all slides and agrees that the original diagnosis, from the specimen taken by him, should be myxolipoma, benign.) (Figs. 28 to 35.)

Leiomyomas. These tumors can occur in the mediastinum, but diagnosis is impossible until biopsy is performed, preferably at the time of total excision of the mass. It is important to remove them because of the possibility of sarcomatous degeneration in this type. An interesting case in our series showed multiple pressure defects of almost the entire intrathoracic esophagus, with intact mucosa on esophagoscopy. At operation 14 intramural extramucosal tumors of the esophagus were removed, which proved to be leiomyomas on microscopic section.

CASE 23. C. S. A 23 year old white male complained of substernal pain on swallowing of 2½ years' duration and a sensation of pressure defects in the esophagus. Esophagoscopy confirmed the multiple pressure defects and stated they were all extraluminal. No evidence of ulceration in any area was seen. Physical examination and laboratory studies were within normal limits. Thoracotomy showed multiple tumor nodules along the entire length of the thoracic esophagus, varying in size from about 4 centimeters to 1 centimeter. One of these masses was removed for a frozen section. Pathological report was leiomyoma of the esophagus. A total of 14 esophagus tumors were removed, the tumors were located in and beneath the musculature of the esophagus, but caused no erosion of the mucous membrane. At no time was the lumen of the esophagus entered. Recovery from the operation was uneventful. Pathological diagnosis: multiple leiomyomas of the esophagus. (Figs. 36 to 39.)

Xanthomas. These tumors occur in the mediastinum as elsewhere in the body. They are considered benign, but may go on to form xanthosarcomas. Heuer and Andrus (26) collected only 10 cases of this type in 1940, including 2 of Dr. Heuer's. The tumors occurred only in adults and all 10 were successfully removed. It is questionable that these tumors should be considered as a separate type as they seem to be more of a degeneration process in tumors such as lipomas and fibromas.

Chondromas, Chondromyxomas, Chondromyxosarcomas. These tumors originate from cartilage, which is found adjacent to the mediastinum in the sternum, costal cartilages,

and articular surfaces of the spine and costovertebral junctions. They are important in that they attain great size and may metastasize, even though benign on microscopic section. Heuer and Andrus (27) found in the literature since 1926 only 14 that involved the mediastinum. Surgical removal is indicated, as they do not respond to radiation therapy and resection is facilitated by the infrequency of invasion of surrounding structures.

NEUROGENIC TUMORS

Pathological discussions of neurogenic tumors are based on work done by Von Fischer and Kuntz. These tumors arise from the sympathetic nervous chain or its anlagen and are manifestations of the development from the original medullary epithelium. As the cells migrate from the ganglionic crest, they may form cell "rests" at various stages in their development which proliferate to form the neurogenic tumors. Using the chart published by Andrus in 1937, a simplified method of showing the origin of the thoracic neurogenic tumors is presented:

Medullary epithelium	→Neuroepitheliomas
↓	
Ganglionic crest	→Neuroepitheliomas
↓	
Migrating undifferentiated cell	→Neurinoma (schwannoma)
↓	
Sympathicoblast	→Sympathiocoblastoma
↓	
Neuroblast	→Neuroblastoma
↓	
Sympathetic ganglion cell	→Ganglioneuroma
Primitive mesenchyme	
↓	
Fibroblast	→Neurofibroma (Neurinofibroma)

Neurofibromas. The origin of these tumors from one of the three nerve sheaths caused Verocay to suggest the term "neurinofibroma." These tumors are thought to come from the perineurial or endoneurial fibrous tissue and are distinguished from the tumors of the sheath of Schwann which are characterized by elongated fusiform cells with "pallisading" of the nuclei. The two types of tumors are frequently confused. Heuer and Andrus (27) collected 20 authentic cases of intrathoracic neurofibroma and added 1 case. They also collected 19 cases of neurinoma (schwannoma), showing that the relative frequency is about equal. We can add 3 cases of neurofibroma and 1 case of schwannoma, all originating in the mediastinum.

CASE 24. J. A. V. This 33 year old white male complained of dull pains around his heart, associated with mild shortness of breath, of 8 months' duration. Five months after the onset of his complaint, chest roentgenogram showed a mass in the left mediastinum which seemed to be contiguous with the aortic outline. Fluoroscopy and electrocardiogram ruled out aortic aneurysm. Generalized lymphadenopathy developing 7 months after onset of his complaint complicated the picture, and the possibility of a lymphoblastoma was entertained. However, axillary biopsy showed reactive hyperplasia. Heterophile antibody agglutination was positive, and a diagnosis of mononucleosis, infectious, was confirmed. Following recovery from infectious mononucleosis, thoracotomy was performed which showed a tumor mass approximately 8 centimeters in diameter lying beneath the mediastinal pleura just above the superior aspect of the arch of the aorta. The left subclavian artery was stretched tightly over the tumor mass. The tumor was enucleated by blunt and sharp dissection, and from gross appearances was completely removed. Recovery from surgery was uneventful. Pathological report was neurofibroma, benign, posterior mediastinum, left.

CASE 25. L. T. H. This 31 year old white male had a routine chest roentgenogram which showed a mass in the left posterior mediastinum. Except for a dry cough for a number of years, history was completely negative. Physical examination and laboratory studies were negative except for the roentgenograms which showed a dense rounded mediastinal tumor in the posterior mediastinum on the left, extending from the upper border of the sixth rib posteriorly to the lower border of the ninth rib posteriorly. Thoracotomy was performed and a tumor was removed from the posterior mediastinum on the left; several pedicles which apparently represented nerve tissue extended into the intercostal spaces. These pedicles were clamped and ligated, and the tumor was removed. Recovery from operation was uneventful. Pathological studies showed an egg-shaped tumor mass 7½ by 6 centimeters with a smooth, greyish yellow capsule. Microscopic section showed the tumor to be composed of fibrous tissues, nerve fibers, and xanthoma cells, but no true myxomatous tissue. Diagnosis: mesenchymal tumor including nervous and fibrous tissue, and xanthoma cells, benign, predominantly neurofibroma.

CASE 26. D. L. This 22 year old white male was discharged from the Navy in November, 1945. He was told he had a tumor in his chest and should have a recheck in 4 months. He later applied for work in a steel mill and the tumor was seen again on roentgenograms. He was advised to have it removed imme-

Fig. 48.

Fig. 49.

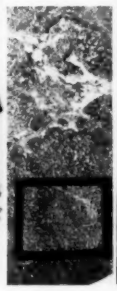

Fig. 50.

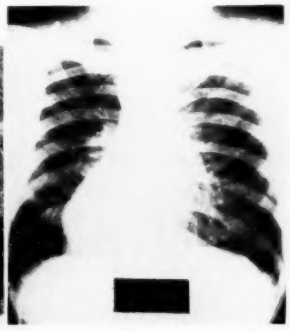

Fig. 51.

Fig. 48. Preoperative roentgenogram, no evidence of enlarged thymus. Case 30.
Fig. 49. Gross specimen, thymus removed *in toto*.
Fig. 50. Showing lymphoid tissue and Hassall's body.
Fig. 51. Postoperative roentgenogram after mediastinotomy through sternum.

diately. On admission to the hospital patient had no complaints. Physical examination was essentially negative. Laboratory studies were negative except for the roentgen-ray examination which showed a left posterior mediastinal tumor arising from the region of the 6th thoracic foramen. There was a very slight decalcification on the inferior margin of the 6th thoracic pedicle which suggested a dumbbell type of neurofibroma. Thoracotomy was performed and a solid mass in the left posterior mediastinum was easily removed. There was no pedicle extending to the 6th thoracic vertebra. Recovery from surgery was uneventful. Pathological report showed a spherical 4 centimeter mass with a smooth and glistening surface. Microscopic section showed the tumor capsule to be composed of coarse hyaline connective tissue, and the tumor was composed of interlacing bundles of elongated eosinophilic cells with hyperchromatic nuclei. In many areas palisading was marked and fibers were delicately fibrillar. No evidence of malignant changes noted. Diagnosis: neurinoma (schwannoma), degenerating, mediastinum, left.

CASE 27. F. R. B. This 31 year old white male was completely asymptomatic. Routine roentgenogram was read as showing "clot of the upper lung field on the right." Admission physical examination and routine laboratory studies were negative. Roentgenograms showed a lobulated mass in the superior mediastinum on the right. Bronchoscopy was negative. Thoracotomy revealed a firm tumor mass at the level of the second, third, and fourth ribs in the posterior mediastinum. It was removed by blunt and sharp dissection. Recovery from surgery was uneventful. Pathological report showed a reniform encapsulated mass weighing 62 grams measuring 8.2 by 3.8 by 3.3 centimeters enclosed by a thin fibrous capsule. One surface has three transverse poles dividing it into three almost equal lobules. The cut surface showed the smallest lobule to be greyish translucent and uniform; the two larger lobules contained indefinitely outlined opaque orange yellow areas suggesting xanthomatous change rather than caseation. The rest of the tissue was greyish translucent. The middle lobule showed cystic degeneration and hemorrhage. Microscopic examination showed a fibrous capsule enclosing the tumor. In addition there was fat outside the capsule where the tumor was detached from its bed. Other sections showed thin pleura covering the capsule where it bulged into the pleural space. The tumor was composed of interlacing bundles of spindle nerve cells with some areas where palisading of nuclei was visible. Many engorged capillaries were present in the tumor. Many areas of edema with small cystic spaces were found. Other areas showed well marked cystic degeneration with hemorrhage in tissue around the small cysts. In one such area there were collections of closely approximated, hyalinized thick walled vessels suggestive of sclerosing angioma. The opaque, orange, yellow areas seen grossly were areas of xanthomatous degeneration lying close to the capsule. The nuclei of the rather plump spindle tumor cells varied in size but mitosis was not seen. In the areas of cystic degeneration there was some round cell infiltration. Impression: This was a neurofibroma with areas suggesting neuroma with cystic degeneration, some hemorrhage, and xanthomatous degeneration. Diagnosis: neurofibroma, intrathoracic mediastinal, benign. (Figs. 40 to 43.)

Ganglioneuromas. In 1932 Scott and Palmer reviewed the tumors of the peripheral sympathetic system and adopted a classification listing the tumors according to degree of differentiation. This was similar to the work done by Von Fischer in 1922. Ganglioneuroma lies with pheochromocytomas and astrocytomas in the completely differentiated group. There is

a very low tendency toward malignancy, varying inversely with the age of the patient. Heuer and Andrus (27) collected 68 cases of intrathoracic ganglioneuromas including one of their own. Seventy-four per cent of those cases with stated age were in children under 10 years. The prognosis is good if the tumor is surgically removable. We have 2 cases of this type to present.

CASE 28. A. P. T. This 22 year old white male first noted chest symptoms of dyspnea, dizziness, and pain in the left chest approximately 8 years previous to admission. He was sent overseas where he participated in combat duties with an infantry regiment. Because of chest symptoms, roentgenogram examination of the chest was performed, and a diagnosis of tumor, type undetermined, was made. On admission his only complaints were dyspnea, mild, and intermittent mild pains in the left chest. Physical examination was completely negative except for dullness to percussion and absent breath sounds over the posterior left chest up to the level of the 7th rib. Roentgenogram examination showed a large, sharply circumscribed opacity occupying the lower one-third of the left lung field. There was no evidence of erosion of bone. Exploratory thoracotomy showed a large, firm tumor mass occupying the posterior portion of the thoracic space. The tumor was densely adherent to the posterior chest wall at the level of the 7th to the 10th rib. It was lobulated and had a consistency of a neurofibroma or a ganglionic neuroma. It was entirely covered by pleura. The tumor was removed by blunt and sharp dissection, and it was found to be originating in the posterior mediastinum on the left where a large branch of the aorta entered directly into the tumor mass. Recovery from the operation was uneventful. Pathological report showed a non malignant neoplasm—neuroma, ganglionic, of left posterior mediastinum.

CASE 29. H. A. N. This 19 year old white male was completely asymptomatic. While he was undergoing routine examination for re-enlistment for the regular Army, a roentgenogram was taken which showed a mass just to the right of the heart and seemed associated with the cardiac shadow. It was thought at that time that the patient had a "cardiac condition." Cardiac studies were negative however and he was returned to active duty. Five months later he was admitted to a regional hospital because of frequent "blackout" episodes. These attacks came on rapidly and were explained by the patient as sudden "blacking out" during which time he would fall to the floor but would not lose consciousness. These episodes would last about 1 hour accompanied by generalized weakness. The attacks were followed by severe frontal headache lasting 5 to 6 hours. Chest roentgenograms taken at that admission showed the mass to be extracardiac in origin. He was transferred to this hospital for further treatment. Routine laboratory examinations were within normal limits. Roentgenograms of the chest revealed a widening of the posterior mediastinum on the right which was very sharply outlined laterally. Fluoroscopic examination revealed no pulsation and no connection with the cardiac shadow. Examination of the esophagus by means of barium by mouth revealed no displacement or abnormality of the esophagus. The mass on the right had more of the appearance of an encapsulated pleural fluid pocket medially than that of a tumor mass. The complaints of "blackout periods" ceased and neurological clearance was given. Exploratory thoracotomy showed a large tumor mass in the posterior mediastinum extending into the posterior gutter of the right chest which was removed by blunt and sharp dissection. Postoperative course was uneventful. Pathological examination showed an oval encapsulated tumor weighing 240 grams and measuring 15 by 9.5 by 5.5 centimeters. The capsule was thin, permitting underlying pale, greyish yellow tumor tissue to be seen. A paper thin, smooth membrane covered the "free" surface and represented the stretched mediastinal pleura. The "attached" surface was rough, covered by a ragged sheet of fibrofatty tissue extending from one pole to within 3.5 centimeters of the opposite pole and from one border to within 2 centimeters of the opposite border. Cut surface bulged and had a translucent appearance and slippery mucinous feel of myxomatous tissue. Cut surface consisted of indistinctly lobulated, translucent, rubbery, dirty greyish, yellow tissue bulging as distinct nodules which occupied almost one-half and extended into the opposite half for 6 by 3.5 centimeters. Between these firmer areas is more flabby, greyish, tan tissue. Fine, white, fibrous streaks traversed the tumor. Vessels were not visible. There was no gross hemorrhage or necrosis. Microscopic section showed variation of tumor tissue in different areas. In some areas near the surface it was composed of definitely outlined, small nerve bundles separated by an edematous, fibrillary stroma. There was further tearing apart of the nerve bundle so that irregular bands of nerve fibrils irregularly arranged were scattered in the mucinous edematous stroma. Solitary ganglion cells and groups of ganglion cells were scattered here and there through the tumor, and in some areas the tissue was quite suggestive of ganglion having been included in the tumor. Several fairly large nerves were buried in the tumor. The ganglion cells showed varying degrees of degeneration; some had fenestrated borders; satellite cells were frequently seen surrounding the finely granulous cytoplasm of a ganglion cell in which no nucleus was seen. Only occasionally were definite ganglion cell nuclei recognizable. The loose fibrillary meshwork filled with edema fluid which supported the nerve bundles did not appear to be myxomatous tissue but was rather a mucinous degeneration of the stroma. Impression: Ganglioneuroma arising apparently from the paravertebral ganglion showing extensive mucinous degeneration. It appeared benign and grossly was completely removed. Diagnosis:

Fig. 52.

Fig. 53.

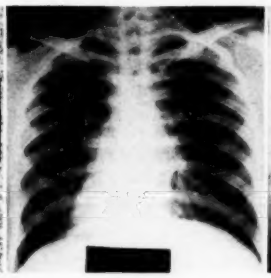

Fig. 54.

Fig. 55.

Fig. 52. Preoperative roentgenogram showing thymic tumor. Case 31.

Fig. 53. Showing alveolar arrangement of tumor cells.

Fig. 54. Postradiation roentgenogram, posteroanterior. No evidence of tumor.

Fig. 55. Postradiation roentgenogram, lateral.

ganglioneuroma, paravertebral, intrathoracic, posterior mediastinum, right, benign. (Figs. 44 to 47.)

Neuroblastomas and neuroepitheliomas. These tumors are examples of the more malignant types of neoplasms derived from the nervous system. In the thorax they are most frequently seen in the mediastinum because of the concentration of sympathetic nervous elements in that area. Although malignant, good results can be obtained by surgical removal when the tumor is localized.

PRIMARY TUMORS OF THE THYMUS

There is considerable confusion in the literature regarding classification of the tumors of the thymus. Pathologically, the tumors fail to fall into well defined groups, making classification a very controversial subject. Indeed, the reports of the tumors sometimes fall into groups according to nationality. Ewing states, "It is significant that the carcinomas have been recorded almost entirely by French observers, while practically all the German reports are of sarcoma." The authors cannot alleviate the confused situation; we are mentioning these tumors merely to be considered in differential diagnosis.

Benign thymomas. The present knowledge of the relationship between myasthenia gravis and tumors of the thymus is sketchy. Following the work of Blalock, the surgical approach to the treatment of the disease has been attempted in some cases, but the results have been far from conclusive. Viets reported the cases of 15 surgically treated patients: 4 showed thymomas, 3 showed thymus hyperplasia, and the rest were normal thymuses. One of the patients with a normal thymus had complete remission of the symptoms of myasthenia gravis. Of the 4 with thymomas, there was no indication that they were more improved than those with hyperplasia or those whose thymus was normal. Since neostigmine has been so successful in the treatment of most cases of myasthenia gravis, it is well to take the conservative view and defer surgery except in those patients who show an enlarged thymic shadow on x-ray examination. We have one case of thymus hyperplasia which showed improvement following thymectomy.

CASE 30. H. H. W. This 28 year old Japanese male had been complaining of diplopia, bilateral ptosis, weakness of the jaw on biting, and hoarseness and vocal fatigue, increasing in severity during the previous 10 months. Three months previous to admission, he was examined at another hospital where the diagnosis of myasthenia gravis was confirmed when the patient improved on prostigmine bromide therapy which was given every 2 hours in alternating doses of 30 milligrams and 15 milligrams. He also received 3/8 of a grain of ephedrine sulfate three times daily. On this therapy all of his symptoms improved except the diplopia. He was transferred to this hospital for thymectomy. On admission here, physical examination showed a moist skin, pupils reacted normally to light and accommodation. There was a marked ptosis on the left, and moderate ptosis on the right. There was an apparent, slight internal strabismus. There was some weakness of the neck muscles, and some weakness of the muscles of the upper extremities more pronounced on the right in the extensor groups. All other findings were within normal limits. Laboratory examination was within normal limits except for the white count which showed 21,000 white cells with 86 per cent polymorphonuclears. Roentgen-ray examination on

admission was negative. Previous to surgery, the prostigmine therapy was discontinued for 3 to 4 days, then the patient was given 10 grains of quinine orally in the morning and at noon. During the afternoon, he complained of marked weakness of his neck muscles of such proportions that he could not raise his head from the bed. There was also an increase in the ptosis, more marked on the left. Fluoroscopy was performed with a barium swallow showing diminished swallowing time which promptly returned to normal following 1½ milligrams of prostigmine intramuscularly with improvement of the ptosis and the diplopia. Following this diagnostic test, the thymus was removed through a sternum splitting incision from which the patient recovered uneventfully. The pathological report showed an irregularly shaped thymus gland weighing 65 grams with an overall length of 18½ centimeters. Microscopic section showed a diffuse hyperplasia of both cortex and medulla. The cortical endothelial cells were prominent, and the medulla epithelial elements were hyperplastic with unusually large thymic corpuscles. No malignant changes were noted. Diagnosis: thymic hyperplasia, benign. Postoperatively there was marked improvement of all the symptoms of myasthenia gravis, but patient continued to have moderate generalized weakness and diplopia. It was found that a single dose of prostigmine 0.5 milligram, given intramuscularly before arising, gave him marked improvement in the diplopia and the generalized weakness. Patient was discharged 4 months after thymectomy, his general condition markedly improved. (Figs. 48 to 51.)

Malignant thymomas. These tumors have been classified by Ewing as falling into two groups: (1) lymphosarcoma or thymoma; (2) carcinoma. He adds a third group called spindle-cell or myxosarcoma, which is very rare. The first group (lymphosarcoma) he considers as originating from reticulum cells, with the lymphocytes being largely passive. This is the most common type. These tumors may be encapsulated within the mediastinum or may assume invasive properties and metastasize to distant sites. Surgery should be attempted in every case, even if only for biopsy, if the lesion appears localized. X-ray therapy in inoperable cases has been reported as useless but should be attempted in all cases because of the frequent pathological confusion with more radiosensitive tumors. We have one case of thymic carcinoma which has responded remarkably to deep x-ray therapy but the follow-up is too short to evaluate the case at present (12 months after surgery was carried out.

CASE 31. R. C. W. This 20 year old white male had a tumor of the right anterior mediastinum discovered on routine chest roentgen-ray examination at a separation center. The patient had no cardiorespiratory symptoms except for asthma which he has had since the age of 5, and which has been much improved during the past 3 years. Physical examination was essentially negative except for decreased breath sounds, decrease in vocal fremitus, and a few râles to the right of the sternum between the third and fifth interspaces. Laboratory studies were within normal limits with the exception of chest roentgenograms which showed a large anterior mediastinal mass measuring approximately 12 by 14½ centimeters in diameter. There appeared to be flecks of calcium in the wall along the right inferior border of the mass, and the impression was an anterior mediastinal tumor, probably teratoma. A sternum splitting incision was made, mediastinotomy was performed, and a large firm tumor mass was found in the anterior mediastinum. This mass was freed up along the left border, but in several places along the posterior aspect of the tumor it had invaded the pericardium and was densely adherent to the underlying great vessels. Exploration of the vena cava and the innominate veins showed that the tumor was apparently invading the lumen of the vessels. A section of the tumor was taken for frozen section, and the report was malignant thymoma. The mediastinum was closed, and the patient returned to the ward in good condition. Postoperatively the patient received 1800 roentgen units through each of four portals, anteriorly and posteriorly, and 1000 units through each of two portals laterally. At the termination of the x-ray therapy, the mass had reduced remarkably in size so that it could barely be seen by x-ray and fluoroscopy. Repeat x-ray films were taken 5 weeks following x-ray treatment, and there was no evidence whatsoever of an anterior mediastinal tumor. Follow-up at the end of 1 year shows the patient still asymptomatic, and roentgenograms are negative. The pathological report showed large cells with abundant acicular cytoplasm. Nuclei varied markedly in size and shape, but in general were round to oval with distinct nuclear membrane, and somewhat vesicular nucleus. Mytotic figures were occasionally seen. Cells were arranged in small groups separated by narrow strips of hyaline tissue forming a delicate trabecular outline. Diagnosis: carcinoma, thymic. (Figs. 52 to 55.)

Thymic cyst. Cystic disease of the thymus is an extremely rare entity in adults. A few cases are reported in infants; most of them are believed to be secondary to congenital syphilis. Ribbert believed that the thymus consists of a series of epithelial channels, their development being arrested by syphilis which caused the "Dubois abscess" or cyst formation. Chiari agreed with Ribbert's theory, but felt

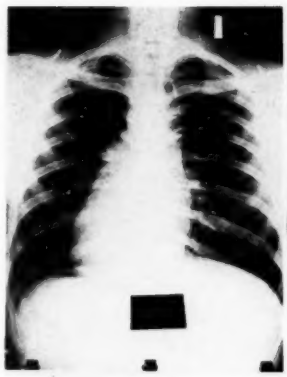

Fig. 56.

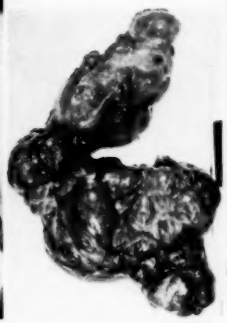

Fig. 57.

Fig. 58.

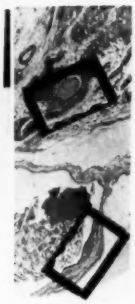

Fig. 59.

Fig. 56. Preoperative roentgenogram. Case 32.
Fig. 57. Gross specimen, intact.
Fig. 58. Gross specimen, opened.
Fig. 59. Showing thymic tissue and cyst wall.

that syphilis was not the only etiological factor.

Previous descriptions of thymic cysts in adults have been limited to small lesions found at autopsy. One case, presented by Kopac (also an autopsy specimen) described a left thymus lobe entirely replaced by a cluster of grape-like cysts. This specimen is similar to our case except his cysts were separate from one another and involved only one lobe of the gland. Kopac summarized the morphogenesis as follows: "The first step in cyst formation is the degeneration and necrosis of the parenchyma in the medullary substance. There is a much greater deterioration of the blood vessels than the degree of involution of the thymus could explain. In these necrotic spaces, fluid accumulation takes place. The surrounding reticulum cells assume a flattened out appearance and form an epithelial layer through which the entire picture assumes appearance of a cyst wall. The cyst increases at the expense of the surrounding parenchyma. As the Strandberg layer is reached by the cyst, the cyst acquires a connective tissue wall. The parenchyma which surrounds the cystic cavities is formed by the cortical substance."

We are presenting a thymic cyst in an adult which completely replaces the gland, is not due to syphilis, and is apparently the first cyst of its type and size to be successfully removed.

CASE 32. T. C. A., Jr. This 22 year old white male was admitted to this hospital for minor burns of his right shoulder and chest. Physical examination was essentially negative except for the minor burns which were treated and healed uneventfully. Routine roentgenogram of the chest showed a widening of the superior mediastinum. Comparison with roentgenograms taken 3 months previously showed that the mass was present at that time although much smaller. Bronchoscopy was negative. Further roentgenographic studies showed a lobulated mass in the anterior mediastinum. Thoracotomy was performed through a posterolateral incision, and a multiloculated anterior mediastinal cyst was removed. Postoperative course was uneventful. Pathological report showed an inverted "V" shaped multicystic tumor weighing 74 grams without fluid content. Filled with 150 cubic centimeters of water, it weighed 240 grams. The specimen was bilobed, one lobe measuring 14 by 2½ by 5 centimeters, and the other lobe measuring 12 by 5 by 7½ centimeters. Microscopic sections showed that this was definitely a polycystic and multicystic thymus. Abundant thymic lobules were still visible in various portions of the walls of the cystic lobes. In the thymic tissue, Hassall's corpuscles were seen with occasional giant cells and xanthoma cells present. There appeared to be a persistence of the epithelial ramifying strands of the fetal thymus. Cystic distention occurred in these. Diagnosis: polycystic thymus. (Figs. 56 to 59.)

PRIMARY TUMORS OF LYMPH NODES

The only characteristic feature of this group of tumors is that they frequently involve only a single group of nodes in the early stages. This fact is important in a discussion of medi-

Fig. 60.

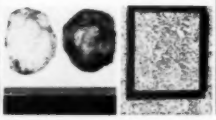

Fig. 61.

Fig. 62.

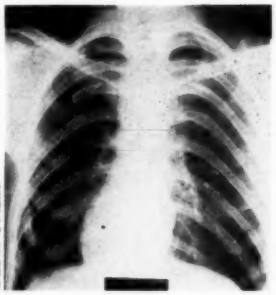

Fig. 63.

Fig. 60. Preoperative roentgenogram. Case 33.
Fig. 61. Gross specimen.
Fig. 62. Showing Reed-cell and marked fibrosis which is replacing the lymphoid and plasma cell elements.
Fig. 63. Postoperative and postradiation roentgenogram.

astinal tumors because that may be the only site where the disease is found. If the disease is generalized, peripheral node biopsy may establish the diagnosis. When mediastinal nodes are the only positive findings, we believe it imperative that mediastinal biopsy be performed, not for medical curiosity, but for aid in planning intelligent therapy and to ascertain prognosis. The mortality of mediastinal exploration is no greater than that of abdominal exploration (44), and some of us believe that morbidity is even less.

Lymphosarcomas. Ewing classifies lymphosarcomas into two groups: (1) reticulum cell sarcoma, (2) malignant lymphocytoma. Although histologically different, the two types are considered as one for clinical purposes. Lymphosarcoma is most often found in a definite chain of lymph nodes, and from there becomes a generalized disease. Primary sites, in order of frequency, are: cervical, mediastinal, retroperitoneal, and mesenteric nodes. In the mediastinal type, the bronchial nodes may be involved with extensions to pericardium or pleura or lung, with marked pulmonary symptoms (Ewing). Extirpation may be hazardous, but at least the attempt should be made because the results from x-ray therapy have been palliative at best. Even with surgical removal, recurrence is the rule.

Hodgkin's disease. In their excellent monograph on this subject, Jackson and Parker showed mediastinal or hilar nodes to be involved in 52 per cent of their 174 cases of Hodgkin's granuloma, with one-third of the cases of Hodgkin's sarcoma showing involvement. It is to be noted that in their 90 cases of granuloma and 10 cases of sarcoma, only 1 case showed mediastinal involvement, with no peripheral lesions. This point is emphasized because in the past a favorite objection to mediastinal exploration was that the lesion may be Hodgkin's. We have treated 15 patients with Hodgkin's during the past year, all with pathologic diagnoses, and in only 2 was it necessary to resort to mediastinal biopsy. One abstract follows:

CASE 33. C. L. B. This 20 year old white male had complaints of weight loss and malaise 6 months previous to admission. At the onset of his complaints a biopsy had been taken from a palpable node in the right inguinal region, and the pathological report was negative. Roentgenograms of the chest at onset of complaints showed an enlargement of the mediastinum, type undetermined. At time of admission to this hospital complaints were minimal. Physical examination was negative. Laboratory studies were within normal limits with the exception of the roentgenogram which showed a diffuse enlargement of the superior mediastinum. Test doses of x-ray therapy showed response to the treatment, and a full course of deep x-ray was given to the mediastinum. Patient was discharged and returned in 3 months, at which time a palpable node was found in the left axilla. Biopsy of this node was performed and a pathological report again was negative. He was discharged again for 30 days, and on return the x-ray films of the chest showed nodular widening of the mediastinum on the left at the level of the first rib anteriorly and also just superior to the left hilus with increase in size in the past 5 months. Mediastinal exploration was performed with uneventful recovery. Pathological diagnosis: Hodgkin's disease, lymphogranuloma type, mediastinal node, left. (Figs. 60–63.)

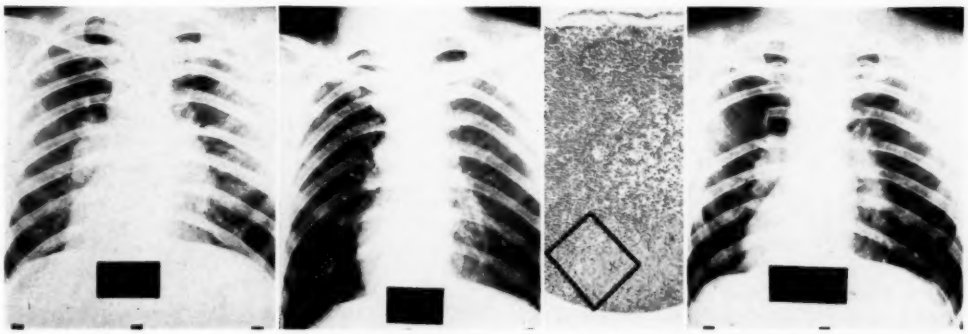

Fig. 64. Fig. 65. Fig. 66. Fig. 67.

Fig. 64. Admission roentgenogram. Case 34.
Fig. 65. After "test dose" of x-ray therapy.
Fig. 66. Photomicrograph showing epithelioid tubercle.
Fig. 67. Postoperative roentgenogram.

Boeck's sarcoid. The mediastinal manifestations of this little known disease frequently simulate the tumors already discussed. Boeck's sarcoid is a pitfall in the common practice of using a "test dose" of deep x-ray therapy to establish the diagnosis of "malignant lymphoma." Riesner (1944) states that over 85 per cent of 35 cases showed mediastinal node involvement, and that 6 of these cases showed practically complete disappearance of the shadows while being watched; half of the total showed some regression. Certainly a "test dose" of x-ray during this regression period would lead to an erroneous diagnosis of lymphoma.

We have 4 cases to present—all were seen in a recent 6 week period. All had extensive medical work-up and were referred to the Tumor Service as "mediastinal tumor, type undetermined." Each one shows a specific point of interest. The first 2 had mediastinal involvement with no palpable peripheral nodes; the third had only one peripheral node found deep in the cervical triangle after repeated careful examinations over a 3 month period (he also had uveoparotid involvement—Mikulicz's disease—since early childhood); and the fourth showing regression of mediastinal involvement to normal over a 5 month period. All cases were proved by biopsy, the first 2 by mediastinal nodes, the second 2 by peripheral nodes.

CASE 34. E. K. C. This 24 year old white male was admitted with a diagnosis of Hodgkin's disease. He had slight chest pain on the left with occasional cough, and a weight loss of 20 pounds in 9 months. Physical examination was essentially negative. Laboratory studies were within normal limits. Exploratory thoracotomy showed multiple nodes in the mediastinum, and a biopsy showed Boeck's sarcoid. Recovery from surgery was uneventful. (Figs. 64 to 67.)

CASE 35. D. C. R. This 19 year old colored male was admitted to this hospital with a diagnosis of Hodgkin's disease. A routine roentgenogram disclosed mediastinal masses, and a diagnosis was made without biopsy. Physical examination on admission was negative. Laboratory studies were within normal limits with the exception of roentgenograms which showed moderate, bilateral, hilar, and superior right mediastinal adenopathy consistent with lymphoblastoma. Exploratory thoracotomy revealed multiple mediastinal masses, and biopsy was made. Recovery from the operation was uneventful except for moderate superficial infection of the wound which responded to conservative therapy. Pathological diagnosis was reported as sarcoid (Boeck's), generalized.

CASE 36. F. A. N. This 27 year old colored male had intermittent dull pain in his right chest with cough and slight amounts of mucopurulent sputum of 1 year's duration. There was a weight loss from 250 pounds to 196 pounds. Roentgenogram of the chest showed a 2 by 5 centimeter mass lying just to the right of the tracheal shadow just above the right main bronchus. There was no evidence of pulsation, and it did not encroach on the esophagus. Physical examination was negative except for a single palpable lymph node in the left axilla. Laboratory studies were negative. Biopsy of the left axillary node showed sarcoidosis, lymph node, axillary, left.

CASE 37. J. L. This 25 year old colored male had a nonproductive cough, fatigue, hoarseness, and pain in the left anterior chest of 4 months' duration. He was admitted to this hospital with a diagnosis of lymphoma, malignant, of mediastinum. Physical

examination was essentially negative with the exception of a single palpable node in a deep cervical chain on the right, and enlargement of the uveoparotid glands, bilaterally. Laboratory studies were within normal limits. Biopsy of the cervical node show sarcoid, lymph node, neck, right.

Endotheliomas. This is a rare type of primary tumor of the lymph nodes, affecting either one node or a group of nodes, but usually progressing to a systemic type of disease. Even when locally removable, it is a recurring malignant tumor. Histologically, it is confused with secondary carcinoma.

PRIMARY AND SECONDARY SARCOMAS

The connective tissue tumors and the neurogenic tumors already mentioned may degenerate to form primary mediastinal sarcomas, notably the fibromas, xanthomas, chondromas, and neurofibromas. Any of the connective tissue in the mediastinum may be the site of sarcomatous growth. Unfortunately, there is no way to distinguish between the benign mediastinal tumors and the malignant on x-ray examination. Total removal is possible in early cases and metastasis is usually late.

Secondary sarcomas of the mediastinum are extremely rare, as hematogenous spread is more frequent, therefore involving the lungs before the mediastinum.

PRIMARY AND SECONDARY CARCINOMAS

The most frequent origin of primary carcinoma of the mediastinum is the thymus, although many times the primary site cannot be determined due to the extent of the lesion. Primary sarcomas are three to four times as frequent as primary carcinomas. Surgical intervention offers no hope, as the lesion is asymptomatic in the early stages and the mediastinal contents are extensively involved by the time exploration is sought. X-ray therapy is palliative in a few cases, but the most effective treatment is section of sensory nerve roots to allay pain.

Secondary carcinomas of the mediastinum usually come from lung, esophagus, or breast, and occasionally from abdominal viscera. Treatment is purely palliative.

CASE 38. V. L. G. This 29 year old white male had recurrent episodes of pain between the shoulder blades of 4 months' duration. The pain was dull, deep seated, and continuous, being relieved only by "leaning up against something." Examination revealed a cyanotic, dyspneic, well developed, young male. Thorax was symmetrical, and expansion was equal. There was supraclavicular and infraclavicular retraction on inspiration. There were small varicosities over the anterior chest. Resonance was impaired at the right base, and breath sounds were diminished in both bases. There were healed biopsy wounds in both axillae. The rest of the physical examination was negative. Roentgenograms of the chest revealed a marked widening of the mediastinal shadow with some evidence of mild atelectatic changes in the lower lobe on the left. Patient received a diagnostic test dose of x-ray therapy over the mediastinum with no evidence of regression of the tumor mass. An anterior mediastinotomy was performed which showed a large tumor mass in the anterior mediastinum which could not be removed. Biopsy was taken. Recovery from the operation was uneventful, but the patient continued to lose weight and strength in spite of heavy doses of x-ray therapy over the mediastinum. His course was progressively down hill, and he expired 38 days following surgery. Pathological report: carcinoma, anaplastic, mediastinum.

CASE 39. W. A. H. This 28 year old white male had a routine chest roentgenogram 6 months previous to admission which was said to be negative. One month later a second routine chest plate was taken and a small tumor mass was found to the right of the midline in the mediastinum. Comparison with the previous film showed a small mass present at that time. During the subsequent 5 months, he was carefully observed with repeated roentgenograms which showed progressive enlargement of the tumor mass. After the fourth month, a trial dose of x-ray therapy was given which was reported as being inconclusive. The patient was transferred to this hospital 6 months after his first roentgenogram in markedly poor condition. He was complaining of mild pain in the right chest, marked weakness, and dyspnea. Physical examination showed marked weight loss and complete dullness to percussion over the entire anterior right chest extending into the axilla and into the right base posteriorly. There was complete absence of breath sounds in this area. There were a few breath sounds coming through over the right chest posteriorly at the apex. Left lung was negative to physical examination. Laboratory studies were within normal limits except for a red count of 4,000,000; a hemoblogin of 75 per cent; and the roentgen studies which showed a fairly well demarcated mass in the right hemithorax apparently originating in the anterior mediastinum and extending laterally resulting in a compression of the right lung and shift of the heart shadow toward the left. Review of the old films showed a 5 millimeter mediastinal mass barely projecting into the right hemithorax present 6 months previous to admission. The x-ray diagnosis was a mass of malignant nature, and from its location, thymic origin was considered.

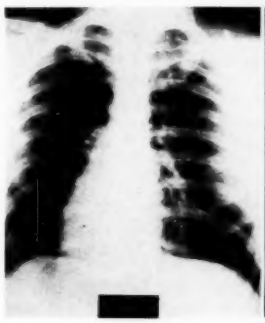

Fig. 68.

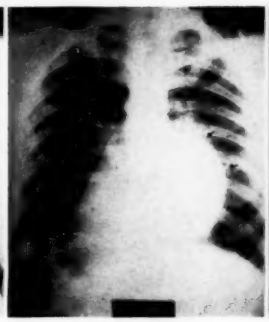

Fig. 69.

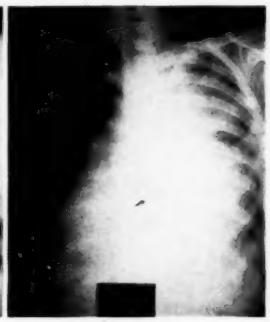

Fig. 70.

Fig. 68. Six months previous to admission. Note right hilar mass. Case 39.
Fig. 69. Two months previous to admission.
Fig. 70. Admission roentgenogram.
Fig. 71. Autopsy specimen showing extent of pulmonary infiltration.

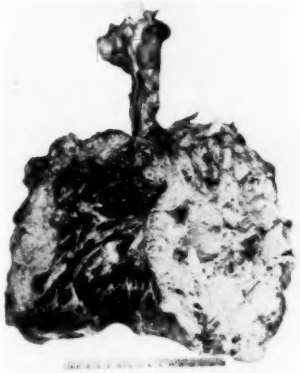

Fig 71.

Exploratory thoracotomy was performed, and an extremely large mass was seen markedly adherent to the right lung and compressing it posteriorly. The mass was entered and found to consist of a moderately thick cyst wall with a tremendous amount of organized hematoma in the center. The hematoma was evacuated from the mass and no bleeding points were found. A section of the wall was taken for biopsy. Thorax was closed, and the patient was returned to the ward in poor condition. Pathological report showed a papillary carcinoma. However, there was a suggestion of endothelial origin, original site undetermined. Patient required numerous thoracenteses to remove the large collection of fluid formed postoperatively. The reaction from x-ray therapy was too severe, so that he received only a few hundred roentgen units over the anterior mediastinum. Death occurred 2 months after surgery. (Figs. 68 to 71.)

CASE 40. P. T. This 51 year old colored male had a persistent cough of 13 years' duration. Ten years previous to admission he expectorated blood for 1 week. He had recurrence again 2 years previous to admission, and 1 year previous to admission, each attack lasting for about 1 week. Four months previous to admission, he had marked weight loss, malaise, and left chest pain, so he was seen by a physician who took chest roentgenograms and told him he had no trouble, so he returned to work. His disabilities continued to grow more severe. Finally a second roentgenogram was taken 4 months after the onset of acute symptoms, and he was referred to this hospital with a diagnosis of mediastinal tumor, type undetermined. Physical examination was essentially negative except for moderate weight loss. Laboratory studies were within normal limits except for the roentgenogram of the chest which showed moderate nodular mediastinal enlargement. Thoracotomy was performed with removal of a mediastinal lymph node for biopsy. Recovery from thoracotomy was uneventful. Pathological report on the biopsy revealed anaplastic carcinoma, original site undetermined. Postoperatively he received 1400 roentgen units to each of four portals, two anteriorly and two posteriorly with complete remission of symptoms. He was discharged for 1 month at which time a second course of x-ray therapy was given, bringing the total roentgen units to 2,150 over each of the four portals. On his third admission, 1 month after discontinuance of the second course of treatment, he was given a

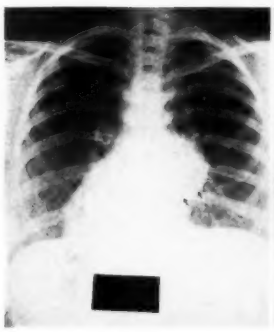

Fig. 72.

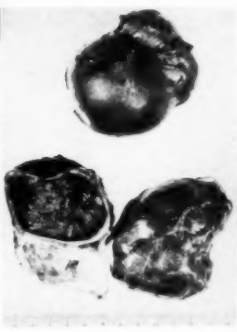

Fig. 73.

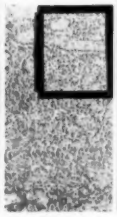

Fig. 74.

Fig. 75.

Fig. 72. Preoperative roentgenogram. Case 41.
Fig. 73. Gross specimen, a roughly spherical mass, 5.5 centimeters in diameter.
Fig. 74. Showing colloid-like follicle and rosette-like tubules.
Fig. 75. Postoperative roentgenogram.

third course which consisted of 2,400 roentgen units over each of two lateral portals. Until this time the patient had been feeling well—at least holding his own except for a single episode of pain directly in the wound, and on palpation a single nodule was found lying in the skin. This nodule was removed, local anesthesia being used and the pathological report showed anaplastic carcinoma, the same type that was removed from the mediastinum. Apparently there had been seeding of the carcinoma into the skin at the time of the original biopsy. Recovery from this minor surgery was uneventful with no recurrence in the wound. Following the third course of x-ray therapy, patient gradually began to fail, complaining of pain over his left chest and left shoulder. He had marked weight loss, and roentgenograms showed a diffuse density in the lower two-thirds of the left lung field. The patient expired 7 months after mediastinal biopsy. Autopsy showed the carcinoma still confined to the mediastinum with postradiation fibrosis and bronchopneumonia at the base of both lungs.

INTRATHORACIC GOITERS

This group of mediastinal tumors is mentioned merely for differential diagnostic purposes. Several goiters in the mediastinum with no connection with the thyroid have been reported. Mason's was located in the posterior mediastinum and was successfully removed by extrapleural mediastinotomy. We have 1 case of mediastinal goiter with no connection with the thyroid. It was located between the bifurcation of the trachea and the base of the heart, extending laterally into the right thorax.

Case 41. I. O. S. This 24 year old white female had a routine chest roentgenogram which showed a mass in the mediastinum. History was completely negative. Physical examination was within normal limits. Laboratory studies were negative except for roentgenograms which showed an ovoid 6 centimeter mass, lying attached to the pericardium in the region of the junction of the right ventricle and right atrium. The x-ray diagnosis was probable pericardial cyst. Thoracotomy was performed and the mediastinal mass was removed. It was lying anterior to the pericardium, and extending upward in the mediastinum to the bifurcation of the trachea. Recovery from operation was uneventful. Pathological report showed a roughly spherical mass measuring 5.5 centimeters in diameter with an attached mass measuring 5 by 2½ centimeters in diameter. On cutting the specimen, considerable turbid old blood exuded under pressure. The large space was filled with friable yellowish-gray fibrin. Attached tumor structure was multiloculated and contained clear straw colored fluid. The tumor was composed of glistening gray tissue. On section of the cyst wall, there was an area of thymic tissue closely associated with fibrous capsule. Extending over the thymic tissue and extending into the cyst was an adenomatous structure with very small rosette-like tubule, and as the cavity of the cyst was approached, these tubules became larger forming increasingly larger follicles containing colloid material. Cells were regular in size and shape with large round nuclei with finely distributed chromatin. The cytoplasm was poorly discerned, but granular and appeared to have a secretory function. No mitotic figures were noted or evidence of manifest malignant change. The tumor was considered to be a benign aberrant thyroid tissue having no connection with the normal thyroid gland and lying completely within the anterior mediastinum. (Figs. 72–75.)

SUMMARY

1. A classification of mediastinal tumors is presented.

2. The various types of tumors are discussed under separate headings.

3. Emphasis is placed on the importance of thoracotomy for pathological diagnosis, with extirpation of the mass if it is operable. Evidence is presented to show that thoracotomy is a safe, rational procedure with no mortality in properly selected cases.

4. Thirty-five mediastinal cysts and tumors are presented, with six additional cases of differential diagnostic conditions.

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A TECHNIQUE FOR PORTACAVAL ANASTOMOSIS (ECK FISTULA)

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THE recent reports of Whipple and of Blakemore and Lord (2) of their experiences in the treatment of patients with portal system hypertension by means of venous shunt operations have created renewed interest in a type of surgery which should be given a trial in these patients whose lives are constantly threatened by massive hemorrhages from the gastrointestinal tract. Whipple's lucid article and Blakemore's (1) subsequent report of the results in 25 operations point out the problem, the indications for these operations, and the results that have been obtained to date by the group working at the Presbyterian Hospital. Knowledge of this subject has come largely from these workers.

Two operations, splenic-renal vein anastomosis and portal vein-inferior vena cava anastomosis, have proved most useful in decompressing the portal system. When portal hypertension exists, pressure readings in this system are frequently 3 to 5 times greater than normal. Everyone is familiar with the routes of collateral circulation which develop naturally by the enlarging of normally small venous communications in an attempt to circumvent portal venous obstruction. Esophageal varices frequently develop, and it is the rupture of such varices that produces alarming hemorrhage. In addition to this hemorrhage factor, ascites may develop in part at least on the basis of portal hypertension although the state of liver function is probably a more important factor in most cases of liver cirrhosis. It can be easily seen that a successful anastomosis of a portal system, in which the pressure is in the neighborhood of 400 millimeters of water to a systemic venous system whose pressure may range from 40 to 80 millimeters of water, should greatly relieve the hazard of these two complications of portal hypertension. Whether splenorenal anastomosis or portacaval anastomosis should be used in a given instance depends upon the site of obstruction. In general, when both can be used as is true in the intrahepatic bed block of liver cirrhosis, the larger portacaval shunt is to be preferred.

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While my own experience with Eck fistula operations is limited, in this communication I wish to describe a method of portacaval shunt which I have used in a patient whose case report follows. The technique to be described avoids complete caval obstruction and is technically not too difficult. Blalock (3) has said that it is not necessary to occlude the vena cava completely during this operation but has not described the method he uses. An early operation in 1913 reported by Rosenstein was performed as a side-to-side anastomosis with intermittent caval occlusion. Complete caval obstruction was the complicating factor in other early operations (5).

An end-to-side anastomosis of the portal vein to the inferior vena cava was performed above the renal veins and the anatomical result may be seen in Figure 1a. Dissection of the hepatic pedicle and the isolation of the portal vein is time consuming. The essentially important features of this anastomosis are two. In Figure 1b it can be seen that the vena cava is never completely obstructed; a free flow of caval blood can pass beneath the clamp which has temporarily isolated a portion of the wide cava. The clamp used is the ordinary Thomas Smith intestinal forcep which has been used for years in the operation of anterior resection of the rectum. It has spring blades and does not injure the tissue. For emergency use, loops of umbilical tape are placed above and below the clamp. The second feature of the anastomosis is the method of suture. The everting suture described by Blalock (4) has been employed in a medial and lateral row as shown in Figure 1c. After completion of the anastomosis and removal of

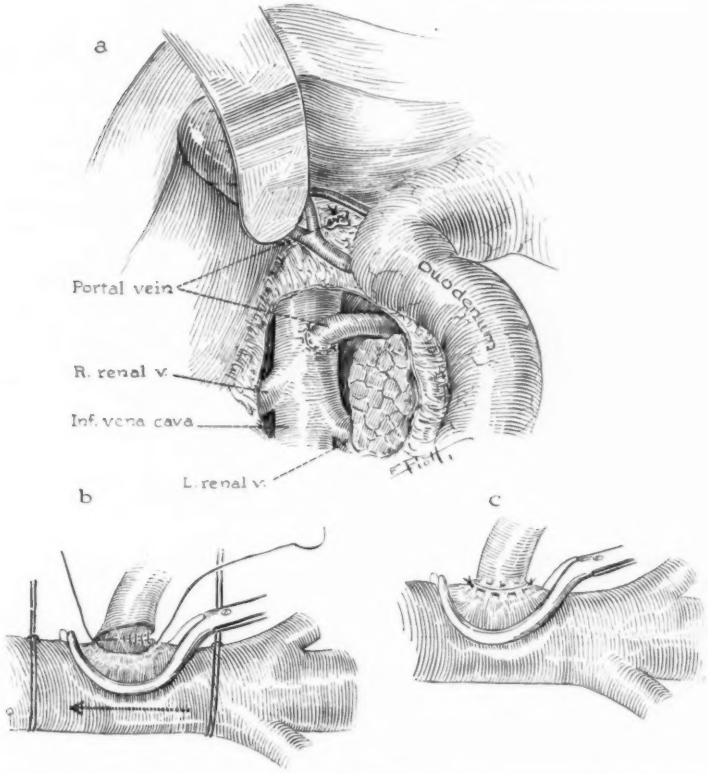

Fig. 1. a, Completed suture portacaval anastomosis. b, Anastomosis of the end of the portal vein to the side of the vena cava above the renal vein entrances with the Thomas Smith clamp in place. Note free caval flow beneath the clamp. c, Anastomosis completed. Note everting type of suture.

the clamp, one small leak was found which was controlled with one interrupted suture. Three zero Deknatel suture was used.

This method of anastomosis has the advantage of not obstructing the vena cava. It can therefore be done almost at leisure. The Blakemore method of nonsuture anastomosis with a vitallium cup which is placed on the end of the portal vein and later secured into the side of the cava by pursestring sutures requires that the cava be obstructed during this maneuver. Complete obstruction of the inferior vena cava, so well tolerated below the renals, can only be borne with safety above the renal veins for an estimated 10 minute period. Longer obstruction incurs serious kidney damage with resulting anuria. On one occasion, I have shut off the vena cava for too long a time in order to repair a rent in this vessel caused by attempting to pursestring a vitallium-tubed portal vein. Death with anuria resulted 5 days after operation. This important time factor in methods which require caval obstruction can be avoided by the method described. Another advantage of this suture method is in its preservation of the full length of the portal vein after its severance close to the liver. Cuffing of the vein over a vitallium tube loses a valuable half inch of this vessel.

The theoretical disadvantage of suture anastomosis is concerned with intravascular clotting at the anastomosis with exposed sutures as the precipitating factor. The non-

suture anastomosis is supposed to avoid this contingency. The pressure differential, however, between the portal system and the vena cava should avoid this complication, since there is effected a shunt, lesser but similar to an arteriovenous communication. These latter fistulas are in the normal course of events very liable to keep open.

It is quite probable that the clamp method of anastomosis described cannot be applied in all cases. When it can, however, it will be found, I believe, to be technically less difficult and less dangerous. The Blakemore tube method on the other hand has been found to be very satisfactory for the group working with this method who have developed great skill in the technique. This type of suture technique, I present as an alternative method.

CASE REPORT

Portacaval anastomosis for portal hypertension caused by intrahepatic portal bed block (cirrhosis of the liver).

H.L., a young man, 24 years of age, was referred by Dr. William Moloney who had attended him for some time for severe gastrointestinal hemorrhages from oesophageal varices, the result of hepatic cirrhosis.

In April of 1944, while in the service, this patient began to complain of weakness, dizziness, and lassitude with occasional fainting spells. These may be interpreted as probably the result of an anemia. On one occasion, he fell off a gun emplacement and was hospitalized with a questionable diagnosis of head injury. In November of 1944, while an Army Hospital patient, he had his first severe gastrointestinal hemorrhage. There was a large loss of blood requiring several transfusions. A diagnosis of splenomegaly, with Banti's syndrome was made and in April, 1945 a splenectomy was performed at the Cushing General Hospital. The patient was subsequently discharged from the service on certificate of disability. In December of 1945, about 8 months after splenectomy, he was admitted to the Carney Hospital with another exsanguinating hemorrhage. This episode was treated by transfusions of blood. Two other hemorrhages occurred before his admission in January of 1945 for study and operation.

On this admission he was found to be in good general health. Physical examination revealed only a slight enlargement of the liver and a healed left abdominal splenectomy wound. There was a mild anemia, the red blood count numbered 3,460,000 per cubic millimeter of blood and the hemoglobin value was 75 per cent. White blood count was 9,100 with a normal differential count. Liver function tests showed good function. Total protein measured 6.7 grams per 100 cubic centimeters of serum with 4.0 grams of albumin and 2.7 of globulin. There was a 15 per cent retention of bromsulfathalein in ½ hour, with 10 per cent in 1 hour. Cephalin flocculation test was reported as 2+; the total cholesterol value was 160 milligrams per cent, cholesterol esters 100 milligrams, free cholesterol 60 milligrams. The hippuric acid excretion test was reported as 4.2 grams of benzoic acid excreted in 4 hours. On roentgenologic examination the esophagus was widened and there were well marked varices. A diagnosis of intrahepatic portal bed block with hypertension was made.

On January 27, a portacaval anastomosis was made according to the method described. Cirrhosis of the liver was found and a liver biopsy secured. Portal vein pressure measured 400 milligrams of water at operation. The patient was heparinized for 4 days. Postoperative complications included right lower lobe atelectasis, a wound hematoma, and an episode of partial intestinal obstruction, none of which were alarmingly serious.

Since operation the patient has remained well and his liver function is being followed. It remains for time to elapse before an estimation can be made of the value of the operation in his case. Absence of hemorrhages in the future will be practical evidence of successful reduction of portal hypertension.

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TUMORS OF THE ISLETS OF LANGERHANS

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LANGERHANS in 1869 first described the pancreatic "islets" which now bear his name and Nicholls in 1902 observed an adenoma arising from these structures. Nevertheless it was the discovery of insulin (4) and its production by certain of the islet cells which led investigators to wonder about hypoglycemia resulting from hyperinsulinism with its possible relationship to islet cell hyperplasia. In 1924 Harris suggested that an excess of insulin in the blood might be brought about by the presence of a hyperfunctioning tumor of pancreatic islet cells. Three years later his prediction was fulfilled when Wilder and co-workers recorded the first instance of such a tumor. Even though their tumor was a carcinoma with hepatic metastasis, a finding in itself unusual, they were able to demonstrate, by biochemical means, that the cells, although undifferentiated, elaborated insulin in large amounts. Since 1927 an increasing number of publications dealing with benign and malignant neoplasia of this type has evidenced a lively interest in the subject. The past 15 years have witnessed, in this regard, the development of many refinements of clinical and laboratory diagnosis. Surgeons through accumulated experiences have learned how and where to search for islet cell tumors, which are frequently small and often multiple. Pathologists have contributed their share of knowledge in the matter of employing special stains (22-24) which have unveiled the important rôle of the so called beta cells in the production of insulin by normal and neoplastic islet cells. They have failed, however, to help their clinical colleagues in the problem of establishing microscopic criteria of "malignancy" in functioning pancreatic tumors.

Abridgment of thesis submitted by Dr. Lopez-Kruger to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine.

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Feeling that in the case of such a rare lesion the analysis of a large series might shed some light on the malignant potentialities of islet cell neoplasms, we undertook comprehensive study of the problem with our prime interest centered on the histopathologic aspects.

MATERIALS AND METHODS

In the 20 years preceding September, 1945, there have been observed at the Mayo Clinic 38 patients who presented the syndrome of spontaneous hypoglycemia on the basis of pancreatic islet cell tumors confirmed at operation or at necropsy. This group of cases constituted the nucleus for the present report.

With the aim of ascertaining the incidence of islet cell tumors, the records of 10,314 consecutive necropsies from the Section on Pathologic Anatomy were studied. These records revealed a total of 44 tumors which had been discovered by routine methods of examining the pancreas. Eight of these tumors were "functioning" and accordingly are listed in the aforementioned group.

For the third phase of our study we are indebted to Dr. Pease, of the Section on Pathologic Anatomy, who furnished us with the results of her careful review of 500 consecutive pancreases studied at necropsy. The material from two pea-sized and six "microscopic" adenomas was thus added to our series in a demonstration of what actually approximates the incidence of these tumors.

With a view to studying the relative number, the limits of size, and the staining properties of islet cells, a number of pancreases were secured at the necropsy table and blocks were taken from various portions. This part of the study was especially helpful in the interpretation of the results of special staining methods outlined in later paragraphs.

From all of these tissues single or multiple blocks were selected so as to include when possible the junction of normal and neoplastic material. When the specimen was surgical

and fresh, portions were placed in 10 per cent formalin and in Bouin's fluid, the former being suitable for routine hematoxylin and eosin stain and the latter for the chromium hematoxylin phloxine stain as recommended by Gomori (22). Older specimens had been fixed in formalin. Blocks cut from these were placed in bottles containing fresh formalin and studied from Mallory-Heidenhain stain preparations. In a few cases in which a stain was desired to demarcate clearly acinar from islet tissue the phosphotungstic acid hematoxylin staining method of Mallory was employed.

CLASSIFICATION

From a careful review of the literature correlated with a study of our slides of pathologic tissue and a subsequent appraisal of the clinical records of our cases, it became apparent that the tumors could be divided conveniently into the following groups: (1) adenomas of islet cells without hypoglycemia; (2) adenomas of islet cells with hyperinsulinism; (3) metastasizing carcinomas of islet cells without hypoglycemia; (4) metastasizing carcinomas of islet cells with hyperinsulinism; (5) borderline malignant islet cell tumors with or without hyperinsulinism. Subsequent paragraphs will deal with the clinical and pathologic aspects of these individual groups and include followup studies on the surgical cases up to, but not including, September, 1945. However, as a prelude to presenting the rather complex histopathologic aspects of the tumors we find it convenient at this point to review briefly our present knowledge of the normal histologic characteristics of the pancreatic islets of Langerhans, particularly as elucidated by the use of newer methods of staining.

HISTOCYTOLOGIC ASPECTS OF PANCREATIC ISLETS

Under the low power objective of the microscope in sections of pancreas stained with hematoxylin and eosin the islets of Langerhans usually stand out as circumscribed, pale, round or irregularly shaped nests varying in size from 25 to 500 microns. Their total number has been variously estimated, 500,000 per pancreas representing a fair average. Their greatest concentration appears to occur in the tail and body of the pancreas, two locations in which the highest incidence of islet cell tumors is also found. Although the islets of Langerhans are fairly well demarcated from the surrounding acini and ducts, no intervening connective tissue capsule, in the true sense of the word, exists and acini and islet cells appear in close apposition. This fact is not surprising when we consider that the islets are formed from ducts (1), although the process, according to most investigators, is normally prenatal (2).

As seen in hematoxylin and eosin preparations using the high power objective, the islets are composed of small, pale, cuboidal, low columnar, or wedge-shaped cells disposed in the form of ribbon-like strands, short cords or alveolar groupings, occurring in pure or mixed pattern forms. These cellular aggregations are separated by fine anastomosing capillary blood channels and the vascularity of the islets stands out in striking contrast to the relatively "bloodless" condition of the surrounding acinar tissue. The blood vessels are accompanied by a certain amount of reticular and fine collagenous connective fibers which impart to the islets, large and small, degrees of lobulation. The thin basement membranes of adjacent ducts and acini along with the endothelium of small blood vessels and the occasional small connective tissue fibers line the islands peripherally and represent the only suggestion of a capsule as seen in our own and other studies.

Individual islet cells were small and of uniform size; each contained a small, round to oval, centrally placed nucleus poor in chromatin and an investing ring of fairly clear cytoplasm. A lack of zymogen granulation and chromidial substance contrasted the pallor of the islet cells with the darker appearance of the surrounding parenchymatous elements. Intimate contact of certain groups of islet cells with sympathetic ganglion cells was observed and Gomori (23) has expressed the belief that these represent special chemoreceptors concerned with the regulation of insulin. As seen in preparations using the Mallory-Heidenhain stain the cytoplasm of islet cells was finely granular. In 60 to 80 per cent of the cells the granules were grayish orange. These were the beta cells, the cells concerned, according to

available experimental and pathologic evidence (13), with the metabolism of carbohydrates. In other words these "beta granules" may be the morphologic expression of insulin content. They are insoluble in water but soluble in alcohol, a matter important in selecting a fixative for studies of pancreatic tissue. Twenty to forty per cent of the cells showed the presence of ruby red granulations, identifying these cells as the alpha cells of Lane and Bensley. These granules are somewhat soluble in water but they can usually be demonstrated in material fixed in formalin. Remaining cells take a sky blue stain and represent the so called D cells.

In fresh tissue fixed with Bouin's fluid and stained with the Gomori (22) chromium hematoxylin phloxine stain, beta granules appeared dark blue, in sharp contrast to the red color of the alpha cell granulations. D cells could not be differentiated from alpha cells by this method.

Mallory's phosphotungstic acid hematoxylin stain colored alpha granules steel blue but did not bring out the beta granulations. However, inasmuch as it colored the zymogen granules of the pancreatic acini a deep blue-black or purple, it facilitated the distinction between acini and islets. It afforded also a means of studying postnatal acinar origin of pancreatic islets. Our investigation by this method did not show cells containing both zymogenic and specific islet cell granulations. Postnatal formation of islets from pancreatic *ducts* is conceded by many investigators.

Using these and other methods of differential staining, wide variations were encountered in the numerical proportions of the various cellular types in the islets and the density of the granulations. Even in presumably normal material margination of granulations and even degranulation were commonly observed. Some of these "aberrations" represent artefacts based on postmortem autolysis. For the best histologic results, employment of perfectly fresh tissue is essential.

ISLET CELL ADENOMAS WITHOUT KNOWN HYPOGLYCEMIA

In a consecutive series of 10,314 necropsies in which the pancreas was made available for study, in 36 cases the presence of one or more clinically silent adenomas of the islets of Langerhans and in 8 cases the presence of "functioning" adenomas was demonstrated. This incidence of 1 in 234 necropsies represents the "routine" average and is considerably lower than the figure cited by Pease, whose 500 consecutive cases yielded 8 solitary nonfunctioning adenomas as a result of a carefully conducted gross and microscopic search for their presence. Twenty-four of the 44 subjects[1] were men and 20 were women. The ages of the patients at the time of death ranged from 27 to 85 years, 91 per cent being more than 50 years of age. Causes of death were varied. Coronary sclerosis and gastrointestinal carcinoma led the list, with no definite clinical or pathologic evidence that hyperinsulinism played even a terminal rôle. Interestingly enough, in 3 of the cases the islet cell tumors developed in spite of the existence of clinical diabetes mellitus.

In these 44 cases there was a total of 52 tumors, 38 being localized in the tail of the pancreas, 3 at the junction of body and tail, 2 in the body proper, and 9 in the head of the gland. In 35 cases the tumors were single, in 8, 2 separate adenomas were present, and in 1 the neoplastic process appeared to be truly multicentric—a sort of adenomatosis. In 5 of the 8 cases of "double tumors," the neoplasms were in close proximity one to another. In 3 instances the tumors were widely separated.

The diameters of the tumors varied from 1 millimeter to 1.5 centimeters with an average of 5 millimeters. Only 3 specimens exceeded 1 centimeter in diameter. Grossly the tumors appeared to be encapsulated and sharply demarcated from the surrounding acinar tissue, although separation could rarely be accomplished along a clear plane of cleavage. As compared with the adjacent tissue the color did not contrast so markedly as did the texture of the cut surface, in which the gross lobulation, so characteristic of pancreatic parenchyma, was replaced by a smooth homogeneity, striking in all islet cell tumors examined in this group.

Histologic features of these 52 adenomas were essentially similar to those detailed for

[1]Thirty-six, plus 8 who had nonfunctioning adenomas.

the "functioning" group of tumors in a subsequent section. Accordingly they will not be described here. Examination of surrounding pancreatic tissue revealed islet cell hyperplasia in 12 instances and proliferation of ducts in 4 cases. Acinar atrophy with fat replacement was noted on 5 occasions and an additional 3 cases showed interstitial fibrosis. In 1 case the phenomenon of squamous call metaplasia of the pancreatic ducts was demonstrated.

ISLET CELL ADENOMAS WITH HYPERINSULINISM

In 1929 Roscoe Graham achieved the first surgical cure of hyperinsulinism when he successfully removed the causative islet cell adenoma (31). From 1929 to September, 1945, we have found in the literature 99 additional and similar examples in which the same result was obtained. Thirty-six other and somewhat similar cases are listed under "personal communication" items and so forth but the data supplied were not sufficient to permit of comparative analysis. A further group of 25 functioning islet cell adenomas has been reported from necropsy studies over the same period.

At the Mayo Clinic from 1927 to September, 1945, in 19 cases a diagnosis of clinical hyperinsulinism was based on the presence of benign islet cell tumors which were successfully removed at operation (12, 25, 36, 37, 46, 55).[1] In 2 additional cases the tumor could not be located at operation and was discovered only after careful search at necropsy. In still another case there existed a condition of diffuse islet cell adenomatosis which was only partially relieved by subtotal pancreatectomy. Thirteen of the patients were female and 9 were male. Their ages ranged from 9½ to 68 years with an average of 41.5 years and with two thirds of the patients listed in the fifth and sixth decades. Symptoms referable to hyperinsulinism had existed for periods varying from 2 months to 18 years. Twelve patients had had trouble for at least 5 years and 5 dated back the onset of their symptoms to periods of more than 10 years. The minimal blood sugar level[2] was less than 50 milligrams per 100 cubic centimeters in 20 of the 22 cases and in 16 it was less than 40 milligrams. A minimum of 20 milligrams was recorded in 1 case. The blood sugar level did not reflect any information as to the clinical duration of the trouble.

In 12 of the 22 cases the tumor was more or less easily identified by the surgeon and removed by simple excision. In 3 cases surgical removal of the body and tail of the pancreas was carried out with the hope that the zone of tissue removed included the causative tumors, which were not palpable at operation. In 1 instance this procedure was successful, a small adenoma being found by the surgical pathologist. In the other 2 cases reoperation was necessary, the adenoma being found and excised locally in one. In the other case the surgical pathologist made the discovery of a small tumor deeply embedded in a resected portion of the head of the pancreas (Fig. 1). In 2 instances total pancreatectomy was resorted to because of undoubted clinical evidence of tumor and the inability of the surgical pathologist to find the adenomas in successively removed portions located deep in the head, close to the duodenum. In 1 of our early cases death of the patient followed an exploratory operation with negative findings. An adenoma involving the head of the pancreas was discovered at necropsy. In another case material from 3 partial resections was devoid of adenomas and the patient continued to suffer from the effects of hyperinsulinism until his death 18 years after the last operation. At necropsy elsewhere an adenoma of accessory islet tissue was found near the duodenum. In 2 cases the surgeon resected suspicious tissue which was reported by the surgical pathologist as being "negative" for tumor. Relief of symptoms prompted us to review the surgical material carefully. Adenomas measuring 2.5 and 4 millimeters in diameter, respectively, were found. These represent the smallest hyperfunctioning islet cell adenomas, with surgical cures, on record. The twenty-second case was one in which multiple resections have been carried out for adenomatosis of the islets of Langerhans. Inasmuch as this case bears some resemblance to several of an unusual nature recorded in the literature (20, 40), a brief description is appended.

[1] Seven of these cases have been reported in the literature.
[2] Folin-Wu method.

Fig. 1. Surgical specimen of resected pancreas showing an encapsulated benign islet cell tumor 0.8 centimeter in diameter located in the head. Benign tumors of this type are in general small and in consequence difficult to locate at the time of operation.

A 34 year old white woman had experienced for 11 years transitory episodes of diplopia, faintness, weakness, and excessive perspiration. At first infrequent and mild, with the progression of time these became frequent and severe. It had been noted that the attacks came on before meals and that they were relieved by the taking of food. Recently the attacks had been complicated by unconsciousness with urinary and fecal incontinence. In several of the attacks there had been convulsive twitchings.

Results of physical examination were essentially negative. Studies on blood sugar during an "attack" brought on by fasting showed a level of 36 milligrams per 100 cubic centimeters of blood. Determinations of calcium and phosphorus gave values of 13.1 milligrams and 2.0 milligrams per 100 cubic centimeters of serum respectively. In spite of negative roentgenologic evidence it was considered that the patient was suffering from hyperparathyroidism as well as hyperinsulinism. Following operation on September 24, 1943, for removal of a pancreatic adenoma there was transitory hyperglycemia. Soon thereafter the previous symptoms recurred and on April 4, 1944, the entire tail of the pancreas was removed for multiple small adenomas which had not been palpable at the time of the first operation. This second operation cured the hypoglycemic attacks and brought the blood sugar to normal levels as determined repeatedly over a subsequent period of 18 months.

In March, 1945, the patient returned for consideration of her parathyroid status. Calcium levels at this time ranged from 12.5 to 13.8 milligrams per 100 cubic centimeters of serum, and phosphorus values varying from 1.9 to 2.5 milligrams per 100 cubic centimeters of serum were obtained. Studies on urinary excretion of calcium while the intake of calcium was approximately 125 milligrams daily demonstrated a "negative balance." There was no evidence of renal calculi or of disease of bone. On March 22, 1945, a typical parathyroid adenoma measuring 2.5 by 1.5 by 0.5 centimeters was found and removed from the anatomic location of the left inferior parathyroid gland. Postoperatively no "chemical" improvement was noticed in the studies of the blood and at the present time the advisability of surgical exploration of the mediastinum is being considered, to climax this most unusual story of probable multiple parathyroid tumors associated with pancreatic insular adenomatosis.

Pathologically, the first pancreatic adenoma removed from this patient measured 1.5 centimeters in diameter, was well encapsulated, and did not differ materially from others described in this series. Atypical beta-like granules were found in abundance. The material from the second operation, on the other hand, showed large zones of pancreatic acinar tissue replaced by a multicentric nodular growth of atypical islet cells. These growths varied in size from microscopic dimensions to nodules 1.5 centimeters in diameter (Fig. 2). At least 8 of the nodules exceeded 1 centimeter in average diameter. Some of the smaller "units" resembled, microscopically, clusters of giant islets; some of the larger resembled ordinary islet cell adenomas. Everywhere there was evidence of compression atrophy of the surrounding acinar parenchyma. Cellular patterns ranged through all the types to be described in connection with the group of "functioning adenomas" with no particular cytologic departure. Apparent lack of encapsulation, degrees of local hyperchromatism and the presence of a very occasional mitotic figure were per-

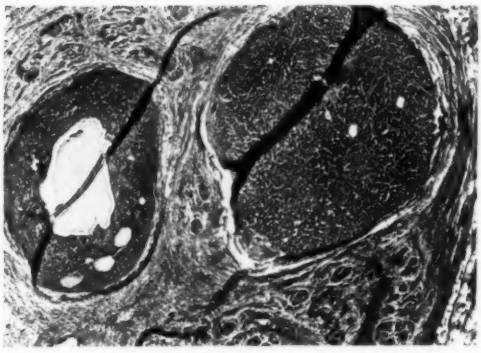

Fig. 2. Benign adenomatosis of islets of Langerhans with hyperinsulinism. Two distinct adenomas (one cystic) are shown. In the vicinity are multiple smaller adenomas and several giant islets (hematoxylin and eosin, ×18).

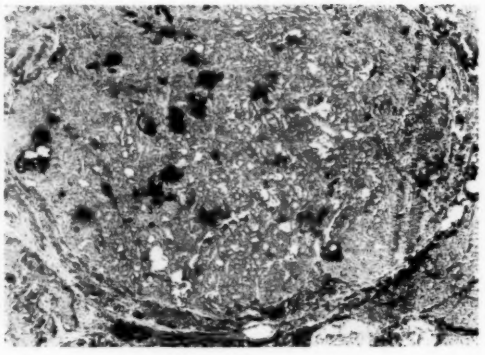

Fig. 3. The illustration includes the major portion of a "functioning" adenoma. The capsule is poorly defined. Regions of calcification are apparent (hematoxylin and eosin, ×19).

haps somewhat unusual features but the condition was adjudged to be benign.

To our knowledge this represents the third case of hyperfunctioning pancreatic insular adenomatosis and the first with associated parathyroid adenoma (probably multiple). The pathologic findings in our case suggest the multicentric origin of certain of these tumors and accordingly the possibility of neoplasia in that portion of the pancreas not removed at operation. Only long follow-up studies on these cases will establish the basis for ultimate prognosis.

Tumors encountered in this group were single in 22 cases and in 1 case multiple—detailed in foregoing paragraphs. Six of the single tumors were definitely located in the tail of the pancreas and an additional 5 were found at the junction of the body and tail of the gland. Nine of the tumors were found embedded deep in the head of the pancreas. An ectopic site was established in 1 case in which repeated resections had failed to reveal the presence of the adenoma and in the remaining case multiple tumors were present in the tail of the gland. Correlating the location of the adenomas with the nature of the operative procedures effecting their removal, it was found that a location other than in the body or tail of the pancreas usually necessitated subtotal or total pancreatectomy in one or more stages. The diameters of the tumors varied from 2.5 millimeters to 6 centimeters (Fig. 3), 16 of the 22 adenomas lying between the limits of 1 and 2 centimeters. The 2 largest measured 3 and 6 centimeters in diameter, respectively, and 4 of the adenomas measured less than 1 centimeter of average thickness. It is most unusual for an adenoma of a size smaller than 5 millimeters to be productive of clinical hyperinsulinism. Two of our tumors were unique in this regard, as pointed out previously. A more or less complete fibrous or fibroelastic tissue capsule delimited 13 of the adenomas from the surrounding pancreatic tissue. In 7 instances the capsule was poorly defined, very thin or present over only a portion of the tumor. In 2, no capsule whatsoever could be demonstrated. It was accordingly felt that the absence of an investing capsule should not negate the diagnosis of an otherwise bona fide example of islet cell adenoma.

On cut surface the tumors had a pinkish or grayish color and more or less homogeneous smooth texture unlike the lobulated appearance of the surrounding gland. The consistency was somewhat firmer than that of the normal pancreas but the difference was not such as to be practically helpful in localizing small and deeply lying tumors of this type. It is not surprising that a fair proportion of islet cell adenomas are found only after careful examination, in the pathologic laboratory, of large segments of resected pancreas. Hyalinization and fibrosis were grossly apparent as degenerative changes in 5 of the tumors in this

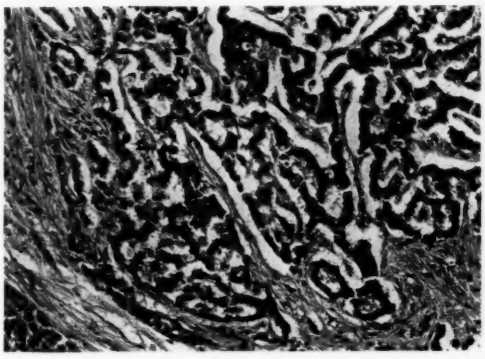

Fig. 4. Histologic details of an adenoma which demonstrated a predominance of the so-called ribbon type of architecture. Note anastomosing bands of large columnar cells which here and there seem to line the thin walled and richly provided vascular channels (hematoxylin and eosin, ×100).

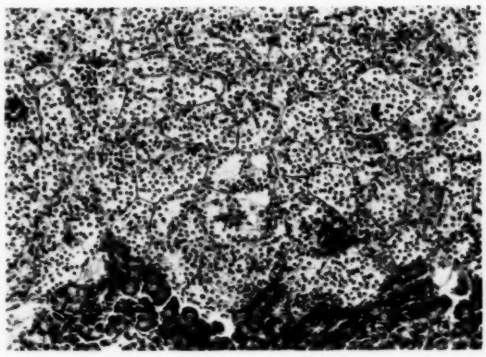

Fig. 5. This adenoma is again poorly encapsulated. Its cells are disposed in tubular and alveolar fashion. The marginal transition between the ducts, the acini, and the tumor cells is more apparent than real (hematoxylin and eosin, ×100).

group. An associated capsular thickening was evident. Extensive hyaline changes appeared to be fairly well correlated with a long preoperative duration of clinical symptoms. In 2 of these hyalinized adenomas calcification was additionally present (Fig. 3), the tumors being definitely gritty. Calcification without gross hyaline change was noted in 3 other instances.

Histologic and cytologic observations. Except possibly in the matter of specific granulation the microscopic observations herein made apply equally to the functioning and the nonfunctioning adenomas. The following notations, however, except when otherwise stated, refer to the incretory group described in this study.

In general, the tumors can be considered structurally in the light of gigantic islets faithfully reproducing on a large scale the normal aspects and structural relations of the islets of Langerhans. In most instances some normal features are exaggerated and repeated over and over, giving the tumor a definite overall histologic appearance. As stained by the ordinary hematoxylin and eosin method and viewed under moderately low magnifications the appearance in all of the tumors was that of typical or atypical "islet" cells disposed in long or short anastomosing cords, ribbons, or strands one to four cells thick. In the majority of the tumors the so called ribbon (trabecular) pattern predominated (Fig. 4), in others an alveolar (Fig. 5), tubular or rosette arrangement was the rule and in still others the appearance of short stubby cell cords imitated the picture of the "simple solid" type of architecture described by Isaji. However, so frequently did the different patterns occur side by side that it was felt that no useful purpose was to be served by classifying them as separate entities. Arrangement of cells was orderly and difference of cell size not appreciable in any given adenoma.

Coursing everywhere among these anastomosing bands of tumor cells were small, thin walled capillary blood vessels. Except in those instances in which fibrous or hyaline material formed a large bulk of the tumor tissue, the adenomas were richly vascular. A delicate fibrous connective tissue framework accompanied the blood vessels and appeared condensed in the form of a thin or thick capsule about the periphery of the tumor, where the surrounding pancreatic acinar and duct tissue was frequently compressed. In some tumors this capsule was incomplete or absent. Focally or diffusely in fifteen tumors the collagenous framework was coarse and heavy with compression of capillaries and cords of tumor cells alike. Regions of hyalinization were always present in these fibrous examples and in 5 instances calcification was found in scattered regions. Hyalinization and calcification in general tended to represent degenerative changes

TABLE I.—HYPOGLYCEMIA: ISLET CELL CARCINOMA WITH METASTASIS COLLECTED CASES FROM THE LITERATURE

Case	Author and year	Age, years, and sex	Minimal sugar, mg. per 100 c.c. of blood	Survival after onset of symptoms and post-operatively	Pathologic data				
					Site, number and size, cm.	Atypia and mitosis	Invasion of vessels	Metastasis	
								Liver	Other sites
1	Wilder and others (56) 1927	40 M	25	21 mo. (Died 1 mo. p. op.)	Tail; single; 8x6x6	+II, atypical granules; frequent, + III	Present	+	+
2	Fedoroff (18) 1931	40 M	27	?	Tail; single; "large"	? ?	?	+	+
3	Judd and others (35) 1934	18 F	45	4 mo. (Died 4 wk. p. op.)	Diffuse; Single; ?	+III; "fairly numerous"	Liver sinus invaded	+	Not described
4	Jacobsen (33) 1934	36 M	25	1–2 yr. (Died 4 mo. p. op.)	Head; single; "grapefruit"	β granules present (?); not seen	Present	+	–
5	Bickel and others (8) 1935	56 M	8	12 mo. (approx.	Body and tail; single; 6	II, multinucleated cells; frequent	?	+	+
6	Cragg and others (15) 1937	41 F	30	9 mo. (Died 6 mo. p. op.)	Diffuse; single; ?	II, liver IV +; scarce	Present	+	+
7	Joachim and others (34) 1938	31 F	25	3 mo. (Died p. op.)	Tail, body; multiple; 6x6x7	II, β granules seen; few	Not described	+	+
8	Seckel (48) and others* 1939	36 M	16	1 yr. (Died 10 wk. p. op.)	Head, body; single; 4x2x2	I, β granules atypical; rare	Not described	+	+
9	Flinn and others (19) 1941	45 F	20	6 mo. (approx.	Head; single; 6	I; rare	Not described	+	+
10	Ballinger (3) 1941	53 M	30	1 yr. (approx.) (Died 4 mo. p. op.)	Aberrant; single; ?	I, no β granules seen; few	Present	+	+
11	Quarrier and Bingham (47) 1942	73 M	21.4	3½ wk.	Tail; single; 3	I; rare	Invaded	+	+
12	Gray (26)† 1942	48 F	27	48 mo. (Died 6 wk. p. op.	Tail; single; 1.8x1.8x1.3	β cell atypical, rare, II; rare	Not seen	+	+
13	Hanno and Banks (28) 1943	68 M	21	19 mo. (Died 2 days p. op.)	Tail; single; 8x8x6.5	No granules seen; rare, multinucleated cells	Not described	+	–
14	Holman and others (case 3) (30) 1943	45 M	27	"Mild 16 yr." "Severe 2 yr." (Died 27 days p. op.)	Tail; single; 12x8x8	Not described; very rare	Not described	+	–
15	Browning (9) 1943	36 M	18	20 mo. (Died 14 mo. p. op.)	Body, tail; single; 9	Cells irregular, II; "numerous, atypical"	Not described	+	+
16	Brunschwig and others (quoted by Gray (26) 1944	32 M	14	5 yr. (Died 2 hr. after last operation)	Body; multiple; 4 and ?	Atypia II, hyperchromic nuclei II; rare	Large veins invaded (first biopsy)	+	Not described
17	Lopez-Kruger and Dockerty 1946	42 M	69	2 mo.	Tail; single; 8	III; many	Invaded	+	+

*Reported also by Brunschwig, Gomori and Cannon (quoted by Gray, 26).
†Reported also by Joslin.
Note: In addition Hanno and Banks (28) have collected seven cases for the literature in which there were no clinical data to establish the diagnosis of hyperinsulinism. Those were: Fabozzi (1903) four cases; Zanetti (1927) one case; Hamdi (1932) one case; Evangelisti (1935) one case. Included also were Duff and Murray's three cases in which hypoglycemia was known to be absent. Frantz (20) reported two cases of carcinoma of islet cells without hypoglycemia, one of them with metastasis. In the other case the patient, apparently free of spread at time of exploration, underwent resection of body and head of the pancreas together with pylorus and duodenum. She is reported not to show evidence of recurrence four years after operation.

affecting tumors of "long standing" as judged by the clinical history. Guttulate deposits of calcium were occasionally noted.

Under higher magnification the individual cells in these adenomas were also strikingly similar to those of normal islets. They were small and varied in appearance from polyhedral through cuboidal, prismatic, and columnar shapes, depending on their position in the cords and lobules. In adenomas with the ribbon type of architecture, the cells tended to be predominantly columnar and to lie in a direction transverse to the long axis of the ribbon. In those tumors in which alveolar clusters and pseudorosettes were prominent, centrally located elements were mostly rounded and polyhedral while peripherally lying cells assumed a columnar appearance. An intimate contact with the vascular capillary network was noteworthy, but invasion by tumor of vascular channels was not observed in this group (Fig. 6). The cytoplasm of the islet cells was small in amount, eosinophilic, and nongranular in ordinary hematoxylin and eosin preparations. In degenerated regions it was sometimes voluminous, vacuolated, and hydropic.

The nuclei were in general indistinguishable from those of normal insular cells, being small, spherical, or ovoid and poor in chromatin. Occasional giant forms were observed. True mitotic figures were very infrequently found but many "doubtful" examples were seen representing pyknotic chromatin particles associated with degenerative changes in the tumors. Nucleoli were small when observed.

Specific granulations. Using the three special stains mentioned in a foregoing paragraph it was found that in two of the tumors typical beta granulations were seen in the cytoplasm of the majority of cells. In 18 tumors, at least a few of the cells contained fine granular material which we considered as atypical beta granulations. In some it was dustlike, in some fragmented and dispersed and in others condensed and marginated as though the cells were undergoing a process of degranulation (Gomori, 22). In fresh material fixed in Bouin's fluid, the granulation always appeared more typical than in the older formalin fixed specimens which furnished us with the bulk of our tumors. In fact the cells in these "older" tumors often failed to show more than a minimum of granulation. Well stained alpha cells were seen in but 2 of the specimens, where they constituted about 2 per cent by actual count. (In the necropsy series they were found more frequently.)

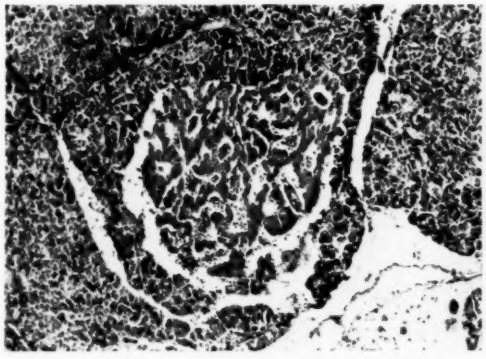

Fig. 6. Projection of tumor tissue into the surrounding pancreatic parenchyma. The cells are somewhat more anaplastic than those depicted in Figures 4 and 5 and there are occasional mitoses. Although there is an entire lack of encapsulation the absence of blood vascular invasion indicates that metastasis is unlikely. The tumor illustrates the salient features of our grade 1 carcinomatous group (hematoxylin and eosin, ×75).

METASTASIZING ISLET CELL CARCINOMA WITH HYPERINSULINISM

When one considers the cellular dedifferentiation which is manifest in the growth of a metastasizing carcinoma it is surprising to note that the anaplastic cells of islet cell carcinomas can produce insulin and clinical hypoglycemia. Yet according to Hanno and Banks, such a clinical effect had been observed in about half of the cases recorded up to 1943. We have abstracted from the literature (Table I) 16 cases of metastasizing and "hyperfunctioning" islet cell carcinomas, of which 4 (10, 15, 35, 56,) have been seen at the clinic. Details of a fifth case (Case 17 of Table I), probably falling into this group, are presented chiefly because of the highly malignant character of the growth, a feature but rarely encountered in reported cases.

A 42 year old man (Case 17 of Table I) was admitted to the hospital in stupor, which rapidly progressed into coma with high fever, death ensuing

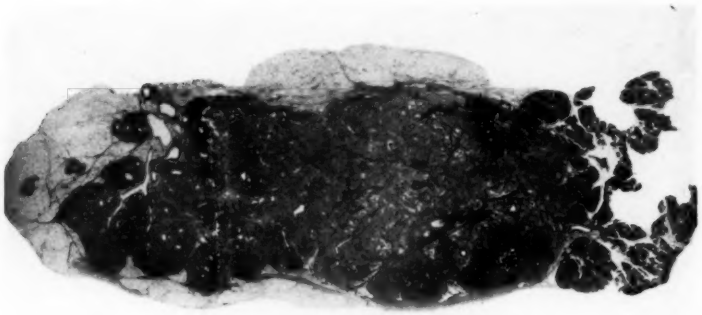

Fig. 7. Metastasizing adenocarcinoma, grade 2, of the islets of Langerhans. Apparent features are the large size and the diffuse infiltration of the tail of the pancreas (hematoxylin and eosin, ×1.4).

within a matter of 48 hours. The history of his trouble had dated back 2 months to an onset with intractable abdominal pain which extended to the lumbar portion of the spinal column and down into the testicles. Morphine was given with only intermittent relief. One month after the onset of the pain additional symptoms in the form of intermittent contractions of different groups of voluntary muscles became manifest. Episodes of rigidity leading to opisthotonos occurred, and these were sometimes relieved by the taking of whisky. Three weeks before admission there developed paralysis of the right facial muscles and weakness of the right arm. Deterioration of the patient's mental status with confusion and delirium were terminal complications.

The picture on examination was that of an unconscious, very restless patient with marked nuchal rigidity and right hemiparesis. The clinical impression was that of meningitis of undetermined origin. Studies of cerebrospinal fluid showed a sugar content of less than 20 milligrams per 100 cubic centimeters. The concentration of sugar taken on admission (nonfasting) was 69 milligrams per 100 cubic centimeters of blood. With a temperature that rapidly rose to 107 degrees F. the patient lapsed into coma and died.

The findings at necropsy, performed 3 hours after death, were remarkable and included carcinoma of the tail of the pancreas (Fig. 7) with involvement of peripancreatic nodes, celiac nodes, liver, left kidney, cauda equina and lumbar portion of the spinal cord. The remainder of the spinal cord and the brain failed to show metastasis.

Microscopically the tail of the pancreas was diffusely involved by a neoplastic process which was infiltrative and in no part clearly delineated by a capsule. The cellular elements showed a marked similarity in form and architecture to the cells of normal islets. Marked cellular atypia, however, was present with many giant nuclei, numerous mitoses and hyperchromatism of many tumor cells (Figs. 8 and 9). Blood capillaries were numerous and thin walled, lying in close proximity to irregular bands of tumor cells which here and there showed actual intravascular invasion. Some large veins likewise demonstrated invasion by groups of neoplastic cells. Special stains employed to substantiate our diagnosis of islet cell carcinoma brought out the presence of fairly typical beta granulations in some of the more differentiated tumor cells. These granules were also demonstrated in the metastatic deposits.

Analysis of all 17 cases of metastasizing and "hyperfunctioning" islet cell carcinomas brings out the following pertinent data: The age of the youngest patient was 18 and of the oldest 73 years with an average of 47.8 years.[1]

Ten patients were in the 40 to 60 year age bracket. There were 12 men and 5 women. In all of 15 cases wherein adequate clinical information was available, spontaneous hypoglycemia was present, usually in severe degree. In 2 cases there was a history of diabetes mellitus preceding the onset of the symptoms of hyperinsulinism. Gain of weight, an unusual symptom in other types of carcinoma, was a unique and contrasting characteristic in these cases. In 9 of the 17 records wherein such data were tabulated, gains ranging from 16 to 65 pounds (7.3 to 29.5 kgm.) were noted. This unusual symptom is a consequence of the tremendous caloric intake designed to prevent the hypoglycemic attacks. The resulting florid obesity of the patients often masked the seriousness of the underlying condition. Jaundice was notably absent in spite of the fact

[1]The average was 34.6 years in our series of 5 cases.

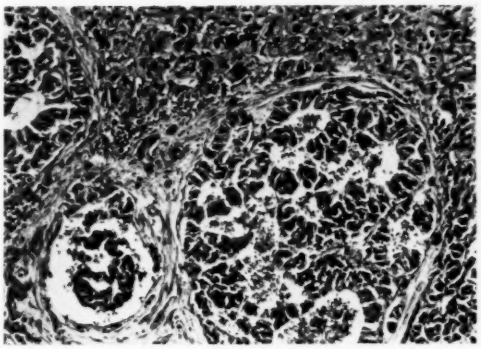

Fig. 8. Same case as in Figure 7, showing invasion of a periaortic lymph node. There is a certain resemblance to normal islet architecture but the cells are hyperchromatic and otherwise anaplastic (hematoxylin and eosin, ×100).

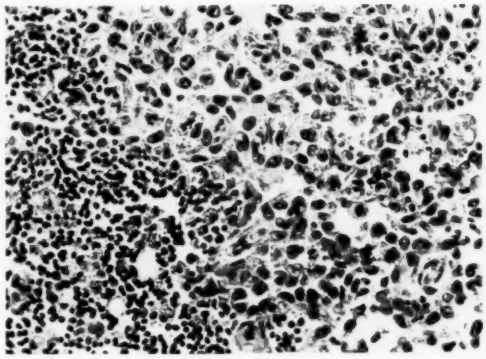

Fig. 9. Same case as in Figure 7. Hepatic metastasis from adenocarcinoma, grade 2, of the islets of Langerhans. Cellular anaplasia and mitoses are apparent features (hematoxylin and eosin, ×210).

that 5 of the tumors occurred in situations near enough to the common bile duct to effect obstruction to the outflow of bile. This is in contrast to the situation existing in cases of ordinary pancreatic carcinoma, in which as a result of perineural invasion by malignant cells a "physiologic" blocking of the common bile duct results.

Average survival after development of these symptoms was about 1 year, with 4 weeks and 4½ years representing the extremes. Surgical procedures employed in these cases consisted of exploration only in 2, exploration plus biopsy in 9 and partial pancreatectomy in single or multiple stages in 2. In 4 cases the condition was discovered at necropsy.

Pathologically in 2 of the cases observed at the clinic the growth was diffuse, involving the entire pancreas; in 1 the head of the pancreas was spared by a growth which extensively involved the remainder of the gland. In one there was diffuse infiltration of the tail only and in the remaining instance the process took the form of two poorly circumscribed nodules 6 centimeters and 2 centimeters in diameter, located at the junction of the body with the tail of the gland. The tumors were all very large compared with their benign counterparts and they lacked any semblance of encapsulation. Involved segments of pancreas were grossly thickened, firm, nodular and often fixed by infiltration of surrounding tissues. Surfaces made by cutting revealed a grayish or grayish pink firm tissue lacking the lobulated appearance of the normal pancreas. Red regions of necrosis and hemorrhage were seen in 3 of the tumors. Metastatic deposits in lymph nodes and liver often showed more extensive necrosis than the primary lesion. The presence of hepatic metastasis was demonstrated in all 5 cases, peripancreatic lymph nodes and omentum were additionally invaded in 3 and in 1 case metastasis was generalized.

Microscopically, in the 5 tumors we were privileged to study, the essential composition was that of islet-like cells disposed more or less in the manner described for benign adenomas but with marked irregularity of size, shape, and staining properties. Outstanding points of difference were (1) the occurrence in all the tumors of mitoses in numbers up to 5 per high power field; (2) the presence of atypical mitoses, some of giant or otherwise bizarre configuration; (3) the presence of large nucleoli in almost all of the tumor cells; (4) invasion of large or small vascular and lymphatic channels observed in every instance (Fig. 10) and (5) the occurrence of necrosis and hemorrhage.

Using Broders' method of grading malignancy, it was found that 3 of the tumors were of grade 2 and 2 of grade 3. The microscopic picture in the metastatic deposits resembled that of the primary lesion. Some of the pulmonary and hepatic secondaries were extremely vascular, with numerous tumor thrombi in venous blood channels. Results of

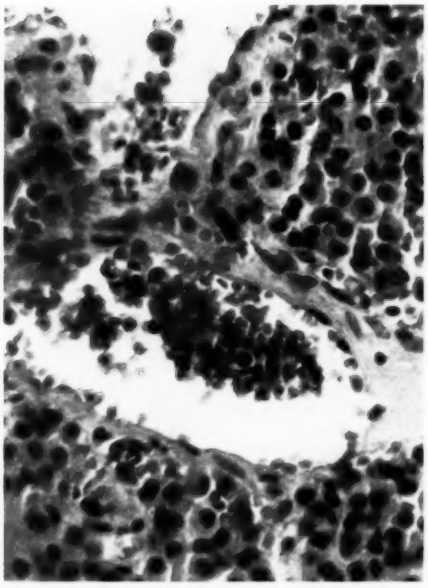

Fig. 10. Metastasizing adenocarcinoma, grade 3, of the islets of Langerhans. The outstanding feature here is the invasion of a large vascular sinus by manifestly malignant cells. This phenomenon of vascular invasion seems in general to be limited to those lesions exhibiting a grade (Broders) of malignancy higher than 1. It may be a very important criterion of "metastasizing propensities" in islet cell neoplasms (hematoxylin and eosin, ×386).

special stains designed to bring out beta and other granulations were indecisive except in the single case previously mentioned. In several of the other tumors atypical dustlike particles were seen in certain of the cells.

Metastasizing islet cell carcinoma[1] is a fatal disease with no patient in the literature surviving for more than 5 years after onset of symptoms. The average life expectancy from available data is 11.9 months. It is accordingly interesting that the case with the longest survival was one of two in which surgical attempts were made to remove the tumor.

Surgical exploration was performed at the clinic in 1930 and a diagnosis of adenocarcinoma, grade 3, was made on some tissue removed from a large nodular pancreatic tumor. With this fresh tissue report the surgeon decided against an attempt at removal. Three months later at another clinic the tumor, still without visible metastasis, was removed and reported as being an islet cell tumor of questionable malignancy. Temporary clinical improvement followed. However, 1 year later at a third operation the original pathologic opinion was confirmed with the demonstration of hepatic metastasis (10). The patient died in December, 1943, following total pancreatectomy with excision of a metastatic hepatic nodule of tumor tissue.

The early history in this case emphasizes the fact that the presence of hepatic metastasis does not always constitute the *sine qua non* of malignancy in certain islet cell tumors, as had been previously supposed. It further emphasizes the possibility of temporarily ameliorating by surgical means the symptoms of hyperinsulinism (25) in patients suffering from the effects of carcinoma of the islets of Langerhans.

HISTOLOGICALLY "BORDERLINE CARCINOMAS" OF THE ISLETS OF LANGERHANS WITH HYPERINSULINISM

We now consider separately a group of functioning islet cell tumors the characteristics of which were such as to place them in the twilight zone between the simple adenomas and the frank metastasizing islet cell carcinomas discussed in a foregoing section. Frantz has reviewed 26 such cases from the literature and has expressed doubt whether some of them constituted truly malignant neoplasms. In general, the tumors have shared certain features of frank carcinomas, such as large size, lack of encapsulation and invasion of surrounding pancreas and of small blood vessels. Cellular anaplasia and the presence of mitotic figures were further features removing the tumors from the "garden" variety of simple islet cell adenomas. Yet, although recurrences have been reported following operation for removal of tumors of this type, metastasis has been lacking. Accordingly it is without surprise that we find them variously designated as adenocarcinoma, grade 1; questionably malignant adenomas; low-grade malignant adenomas and so forth. To the 26 examples cited by Frantz we wish to add pertinent clinical and pathologic data concerning 11,

[1]Hanno, Frantz, and Duff and their co-authors have reviewed the literature on a few cases in which undoubted islet cell carcinomas were not associated with clinical evidence of hyperinsulinism. Discussed also in these reports are several cases in which the evidence for "hyperfunction" of the tumor was debatable. In our series we have not seen an example of this rare type of tumor.

studied from the material seen at the Mayo Clinic. Six of the 11 patients were men and 5 were women. The average age at the time of examination was 37.6 years, the youngest patient being 21 and the oldest 61 years of age. Six were in the fourth decade of life. Symptoms similar to those noted for the benign functioning group had been present for periods varying from 1 to 8 years with an average of 3.5 years. Thus as compared with our benign "functioning" tumors the borderline neoplasms occurred in patients who were 3.9 years younger on an average. Moreover, by the same comparison the symptoms were so serious and progressive that they brought the patient to seek medical treatment in half the time period established for the benign group. These findings are in accord with similar data supplied by Frantz. Minimal blood sugar levels were somewhat higher than those found in the frankly malignant and somewhat lower than those reported in the cases with simple functioning adenomas.

In 10 of the 11 cases operation was performed, the tumors being found with fair ease and excised widely in all instances. In 1 case recurrence of symptoms necessitated a second operation, which failed to reveal residual tumor. The patient continues to have trouble. A second patient suffered from recurrence of symptoms 8 years after removal of his tumor and died shortly thereafter. No necropsy was performed to rule out the possibility of metastasis. Two of the 10 patients died from postoperative complications. The remaining patients have been followed through symptom-free intervals varying from 4 months to 5 years but this group is too small and the periods of postoperative observation are too short for far-reaching conclusions to be drawn as to clinical benignity or malignancy.

One tumor was found at necropsy. Compared with those of the benign series, the tumors were large, with lesions in 6 cases attaining diameters of 2 centimeters or more. Single tumors were encountered in 10 instances and in 1 patient the process was multicentric. The body of the pancreas was given as the location for 6, the junction of the body and tail for 4, and the tail for the remaining 2 tumors.

Grossly, apart from their larger size, the tumors did not differ markedly from their "simple" counterparts except in the matter of encapsulation, which was completely lacking in one and partially lacking in the remainder, 10 of the tumors demonstrating gross invasion of the surrounding pancreatic tissue.

Microscopically all of the tumors showed cellular atypia with a tendency toward large cells. Hyperchromatism of nuclear elements was also universally noted, focally or diffusely, with some of the nuclei assuming giant uninucleated and multinucleated forms. In one neoplasm mitotic figures were very few; in the remainder they were found with moderate ease, averaging perhaps 1 in every 5 "high dry fields" examined. None was atypical or "pathologic" (so-called x and y forms). Nucleoli were in general prominent but the "bird eye" variety so commonly seen in the metastasizing group was rarely observed here. Invasion by tumor tissue of small venous channels was definitely observed in 3 instances. In 1 of these cases, in which there was recurrence of symptoms in 8 years followed by death, metastasis may have occurred eventually. In the second and third instances sufficient time has not yet elapsed to permit of final judgment. Some degree of hyalinization was present in all the tumors in this group and as with calcification—a change noted in 6 of the 12 neoplasms —it tended to increase with the "age" of the tumor as judged by the "functioning" span of its clinical life history.

Examination of 12 tumors using special staining techniques revealed cytoplasmic granularity in 8, in 3 of which the granules identified could be considered as being atypical beta. In 1 case a few alpha granules were seen. The remainder were either agranular or contained a few basophilic fragments of uncertain status.

From a purely cytologic analysis, it would appear that these lesions were of grade 1 (Broders) malignancy (Fig. 6). Unfortunately in support we cannot offer undoubted clinical or pathologic evidence of metastasis. In our metastasizing islet cell carcinomas the grade of the lesion was always 2 or higher and in 1 of these cases metastasis was not presen at the time of the first operation. In the borderline series the grade never exceeded 1 and in

TABLE II.—LOCATION OF TUMORS

	Cases	Tumors	Tail	Junction body and tail	Body	Head	Ectopic
Nonfunctioning group	44	52	38	3	2	9	0
Clinically functioning adenomas	23	22+*	7+*	5	0	9	1
"Functioning" metastasizing carcinomas	5	5	3	2 (diffuse)†			0
"Functioning" but nonmetastasizing carcinomas	11	12	2	4	6	0	0
Total	82	91+*	50+*	12	8	18	1

*In one case multiple tumors, which could not be counted, were present.
†The two diffuse tumors involved the entire pancreas.

only 3 was there evidence of invasion of veins. We feel consequently that venous invasion in any islet cell tumor and cytologic evidence of a grade of malignancy higher than 1 (Broders) are at present the most important microscopic indexes we have by way of correlating the histologic appearance of the tumor with its metastasizing capabilities.

COMMENT

Incidence. Tumors of the islets of Langerhans are rare but the recorded incidence of their occurrence varies considerably, depending on the diligence of the search for their presence. Their frequency has been estimated to be from 1 in 800 to 1 in 1,000, considering necropsy material. Pappenheimer found 5 islet cell adenomas in 4,000 pancreases studied routinely at necropsy. Winters, Gottardo, and McNealy at the Cook County Hospital studied material from 13,000 consecutive necropsies and failed to find a single tumor of this type. The incidence in 10,314 necropsies performed at the Mayo Clinic was 1 in 234 cases, and we have previously mentioned Dr. Pease's experience with a group of 500 glands in which meticulous search yielded 8 islet cell adenomas. Six of these were of such a small size as to be easily missed on routine gross examination of the pancreas. None of Dr. Pease's tumors was clinically "active."

The great majority of functioning islet cell tumors furnish material for the surgical rather than the necropsy pathologist. In this functioning group, it is very difficult to arrive at any definite figures of incidence. Including our own series we have accepted the following as representing the total reported in the period from 1927 to 1945: (1) hyperfunctioning adenomas[1] removed at operation, 113 cases (36 additional with insufficient data); (2) hyperfunctioning adenomas found first at necropsy, 36 cases;[2] (3) nonmetastasizing but cytologically malignant islet cell tumors (combined surgical and necropsy statistics,) 37 cases; (4) metastasizing islet cell carcinomas with clinical evidence of hyperfunction, 17 cases; (5) nonfunctioning islet cell carcinomas with metastasis, 6 (?) cases.

In comparing the different groups the average ages of patients in our series show significant differences; namely, (1) nonfunctioning adenomas, 55+ years; (2) functioning adenomas, 41.5 years; (3) functioning, cytologically malignant but nonmetastasizing group, 37.6 years; (4) metastasizing islet cell carcinoma group, 34.6 years.[3] It thus appears that the more active the tumors cytologically and physiologically the earlier they become manifest.

Men and women were equally affected (41 men and 41 women in the entire series studied.)

Clinical symptoms. These are well known and have not been emphasized in the present analysis. It should be mentioned, however, that, paradoxically enough, the more cytologically dedifferentiated the tumor the more severe the symptoms and the shorter their duration. The paradox of marked gain of weight has particularly been stressed as a symptom in the frank carcinoma group. As previously noted, this symptom has frequently masked the seriousness of the underlying condition.

Location of tumors and incidence of multiple tumors can be seen in Table II.

The high relative incidence of nonfunctioning islet cell adenomas in the tail of the pancreas is paralleled only in a general way when we consider the functioning examples. In the literature 30 of a group of 86 functioning adenomas were listed as occurring in the

[1]In 5 cases hyperfunctioning adenomas or carcinomas have been found in extrapancreatic (aberrant) locations.
[2]The clinical course and symptoms in these cases were identical with those of the previously presented surgical group.
[3]Average 47.8 years for all seventeen cases in the literature.

tail of the pancreas. In the same series the body and the junction of the body and tail were the sites of seventeen and thirteen tumors respectively. The statistical chances therefore of a functioning adenoma arising in a portion of the gland which is not too difficult to resect are about 70 per cent[1]—a practical observation of use to the surgeon who, faced with the undoubted clinical evidence of hyperinsulinism in his patient, is unable to palpate the causative tumor at surgical exploration.

In the matter of multiple tumors the "functioning adenoma" group may again be considered as being representative. Our incidence of approximately 5 per cent stands against 10 per cent observed in the literature (based on 100 consecutive case reports). Both figures are somewhat lower than the incidence of multiple tumors observed in the nonincretory group found "routinely" at necropsy. Although multiple tumors are usually found in the same general region of the gland they may sometimes be widely separated. The surgeon who finds and removes a functioning adenoma has still an important duty to perform in carefully palpating the remaining portions of the pancreas in search for additional tumors.

Even in the matter of locating solitary functioning adenomas of the islets of Langerhans, success does not by any means always reward the primary search. As indicated in our paper, in only 12 of our 19 surgical cases wherein an adenoma was proved to exist, was cure accomplished by the first operation. If we add to the remaining 7 a group in which exploration gave negative results and in which the patients did not return for further surgical operation it appears that perhaps only half of our patients were cured by the first surgical attempt to locate and remove their tumors. Accordingly the present-day surgical tendency is to accept good clinical evidence as being indicative of the existence of a pancreatic islet cell tumor and, failing in a search for its presence, to resect the more easily accessible portions of the pancreas known frequently to contain the tumors. This procedure has proved valuable in our series. Removal of remaining portions of the pancreas can be accomplished later for recurrence of symptoms. Occasionally, as indicated, the causative tumor will involve heterotopic pancreatic tissue.

Individual islet cell tumors were with few exceptions small, a matter which makes for difficulty in their identification at the time of surgical exploration of the pancreas. A diameter of 5 millimeters can generally be taken as the minimum necessary for the production of clinical hypoglycemia. Only 2 of our "functioning" tumors failed to exceed this average size. Rarely do the functioning adenomas attain large size and, when they do, the bulk of the tissue is made up of fibrous and hyaline elements. The frankly metastasizing carcinomas, as a group, are much larger than the benign "functioning" tumors, the cytologically active but nonmetastasizing group providing tumors of intermediate dimensions. The nonfunctioning group range in size from 1 millimeter, providing the smallest tumors in the series.

Texture, color, encapsulation, and so forth. Trends rather than actual measurable gross differences spanned the variations noted in the different groups listed in the foregoing. Frankly malignant islet cell tumors were soft, brown, or brownish red, hemorrhagic, and nonencapsulated, with gross evidence of centrifugal spread into the surrounding normal pancreatic parenchyma. Nonfunctioning tumors and benign functioning adenomas were in general grayish and firm, with fairly clear delineation if not actual encapsulation. Adenomas which proved to be cytologically active or "borderline" tended to be poorly encapsulated, but in general could not be grossly separated as a group.

Microscopically, whether the tumor was benign or malignant, a certain resemblance of the cells and their arrangement patterns to that of normal islet cells made identification of the tumor simple. An intimate relation of tumor cells to a rich network of capillary blood vessels was noteworthy even in tumors which had undergone hyaline and calcareous change. An arrangement of tumor cells in the form of islands, acini, cords, strands, or ribbons was frequently noted, with all pictures

[1]However, the "statistical" evidence has been based on tumors found at operation and the proportion of operations in which the tumor has been found has been about 50 per cent. It is probable that the actual incidence of functioning tumors involving the head of the pancreas is considerably higher than the figure given.

represented in certain tumors. Although the "ribbon" type of architecture predominated, we saw no useful purpose in subdividing the tumors into different types based on these minor differences of cellular architecture. Development of fibroblastic stroma and the formation of an investing capsule varied greatly. Whereas in general the more cytologically active tumors were most poorly demarcated, many benign tumors seemed also to invade the surrounding pancreas. In attempting to determine microscopic criteria of malignancy our efforts were only partially successful, as witnessed by our segregation of a group of "borderline" tumors. It appeared, however, that the metastasizing group possessed the following characteristics: (1) malignancy of a grade higher than 1, as determined by the method of Broders, with cellular atypia, hyperchromatism, loss of "polarity" and the presence of normal and atypical mitosis; (2) invasion of venous channels. The "borderline" group showed cellular activity with mitosis, atypical cell forms and hyperchromatism of a degree commensurate with the diagnosis of carcinoma, grade 1, by the aforementioned method. Invasion of veins, occasionally seen in this group, may place the tumor in question in the category of a possible metastasizing neoplasm. The frankly benign examples showed neither mitotic activity nor venous invasion. From this tentative classification it will be seen that invasion of veins by tumor cells is the all-important criterion which should be sought for as the determining factor in the possibility of extrapancreatic spread of islet cell tumors.

In the matter of using special cytologic stains as a means of differentiating functioning from nonfunctioning adenomas and both of these groups from malignant islet cell tumors, our efforts proved somewhat disappointing. Even dealing with fresh material which yields the best results, we were unable to substantiate the claims of others in this regard. In other words, we found beta granulations in nonfunctioning adenomas and failed to detect their presence in tumors producing marked clinical evidence of hyperinsulinism. The granulations found were, as indicated, often atypical.

SUMMARY

Asymptomatic islet cell adenomas are more frequent than hitherto believed. Routine examination of 10,314 pancreases revealed 44 such tumors and a carefully conducted study of 500 pancreases disclosed 8 tumors (1.6 per cent).

Clinical hypoglycemia originating in neoplastic proliferation of islet cells is a rare disease. Such proliferation can be manifest in 4 ways pathologically: (1) benign adenomas, 70 per cent; (2) islet cell adenomatosis, 2 per cent; (3) histologically malignant but nonmetastasizing islet cell tumors, 20 per cent; (4) metastasizing islet cell carcinomas, 8 per cent.

Generally productive of a clinical history measured in half decades, the adenomas are small, fairly well encapsulated nodules with high degrees of cellular differentiation and no mitosis. The histologically malignant or "border-line" tumors are on an average twice the size of the adenomas and are more vascular and more invasive. The presence of cellular atypia, hyperchromatism, and mitosis is that of a grade 1 (Broders) order of malignancy and is paralleled in a general way with a relatively short clinical history. The possibility of metastasis should be considered in members of this group in which vascular invasion is present. Measured in clinical terms of months rather than years and sometimes of production of a paradoxical gain in weight, metastasizing islet cell carcinomas demonstrate a large size, gross invasive tendencies and metastasis with microscopic evidence of manifestly malignant cells and vascular invasion. In all of the groups positive results using special staining methods will be obtained in some but not all of the tumors. The results do not justify the conclusion that functioning pancreatic insular tumors are beta cell neoplasms.

Statistically speaking, the surgeon can expect to find a tumor in from 50 to 60 per cent of the cases on the first exploration. The presence of multiple tumors (10 to 15 per cent in the benign group including adenomatosis and from 15 to 20 per cent in the borderline and the metastasizing malignant groups) will sometimes decide the necessity of repeated operations in search for the causative tumor (per-

sistence of hypoglycemia after partial pancreatectomy for hyperfunctioning tumor). "Blind" resection of the tail of the pancreas will remove 50 per cent of the tumors; resection of the body as well as the tail will account for about 20 per cent more. Total pancreatectomy will occasionally be necessary for some of the small buried tumors located in the head of the gland, which is the site of about 20 to 30 per cent of the neoplasms. Very rarely (1 to 2 per cent) the tumor will have an extrapancreatic location.

The surgeon performing an operation for the relief of hypoglycemia must be prepared to carry out procedures ranging all the way from simple excision of an easily identified and readily shelled out tumor to total pancreatectomy. These procedures are justified by the complete failure of medical treatment of organic hypoglycemia.

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APPENDICITIS COMPLICATING PREGNANCY, LABOR, AND THE PUERPERIUM

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ACUTE appendicitis is a most serious abdominal disease complication of pregnancy endangering the lives of both mother and child. Crossen and other authorities have stated that 80 per cent of all cases of acute appendicitis complicating pregnancy occur during the first 6 months of gestation. The rarity with which term labor or the puerperium are complicated by acute appendicitis is most striking. Norton and Connell reported but 1 case of term labor complicated by acute appendicitis in 20,000 deliveries at the Margaret Hague Hospital. These same authors collected from the literature and their own hospital records 1,110 cases of appendicitis complicating pregnancy, and from this series they reported only 9 cases as a complicating problem of labor or the puerperium. Thus, it is readily seen that it is highly problematical that any one observer will personally see or attend very many of these cases, nor will he have any large or extensive experience in the treatment of this surgical and obstetrical problem. The recent advancements in surgical procedures, gastrointestinal decompression, intravenous nutrition, and the chemotherapy and antibiotic therapy in the treatment of appendicitis, appendiceal peritonitis, and puerperal sepsis warrant continued review of the approach to this serious obstetrical and surgical problem if the optimum in both surgical and obstetrical treatment is to be achieved.

Historically, we are familiar with the young French surgeon Mêlier's attempt in 1827 to guide the surgical approach to the treatment of inflammation of the vermiform process, only to have the great Dupuytren thwart and crush his efforts. The American pathologist, Reginald Fitz, is credited with solving the riddle of appendicitis in the year 1886. To another American, P. F. Mundé, the famed New York obstetrician and gynecologist, we are indebted for the first report in 1894 of acute appendicitis complicating pregnancy.

During the succeeding 52 years, a considerable volume of medical literature has been presented concerning this surgical and obstetrical problem. Several American and European authors have collected rather extensive series of cases; most notable in this group are the articles by Hilton, Schmid, Jerlov, Heineck, Garcia, D'Erricco, Maes, and Norton and Connell.

The reported incidence of pregnancy complicated by appendicitis varies slightly with the various authors. Mussey and Crane, at Mayo Clinic, reported a high of 2 per cent, Schmid found the incidence in his series collected from the German literature to be 1 per cent. Cosgrove in 1937 reported an incidence rate of but one case in each 1,380 deliveries at the Margaret Hague Hospital. Johnson, in reviewing the problem in Australia, came to the conclusion that the incidence of acute appendicitis in women in the childbearing age is the same rate irrespective of whether the patient is pregnant or not. Findley found that 70 per cent of all women who have appendicitis without operation will suffer from this disease during subsequent pregnancies. Tashiro and Zinninger at Cincinnati General Hospital have verified recently the preponderance of acute appendicitis occurring in the male. They found 66.1 per cent of their series were male patients and 33.9 per cent female.

The accepted clinical signs and symptoms, as well as the established laboratory findings used in making the diagnosis of acute appendicitis, are considerably altered or masked in the presence of pregnancy. As early as 1905 Fueth called attention to the anatomical displacement of the cecum and the appendix

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during pregnancy. The roentgenological studies of Baer, Reis, and Arens of this country, and Guthman and Staehler of Germany have confirmed this displacement. Usually, lateral and cephalic displacement begins at the end of the third month of gestation, and by the end of the sixth month the appendix and cecum are no longer pelvic organs, but rather abdominal organs. Their return to the normal anatomical position in the pelvis occurs between the tenth and twelfth postpartum days. This displacement results in the masking of the signs of muscle rigidity, rebound tenderness, psoas spasm, maximum tenderness over the McBurney point, and acute tenderness in the iliac fossa elicited on rectal examination.

Urinalysis during the early stages of the acute phase of cystitis or pyelitis often reveals little or nothing of a pathological character. Hence, the predilection to right-sided pyelitis and hydroureter complicating pregnancy assumes added significance in the differential diagnosis with acute appendicitis, particularly after the sixth month of gestation.

Nausea and vomiting of pregnancy are difficult to distinguish from that caused by peritoneal irritation associated with an acutely inflamed appendix. Tashiro and Zinninger found 41.9 per cent of the patients with acute appendicitis presented histories of nausea and 67.1 per cent histories of emesis. Constipation and the resultant use of laxatives during pregnancy makes the evaluation of the gastrointestinal tract activity even more confusing.

Homans states that a leucocytosis of between 10,000 and 20,000 is usually associated with acute appendicities. Tashira and Zinninger found in their series that the leucocyte count with acute appendicitis averaged 15,800, and with perforation 15,100 to 17,400. Virchow's "physiological leucocytosis of pregnancy" has been reported by Carey and Litzenberg to be between 8,700 and 10,000, rarely exceeding 12,500. Baer, on the other hand, has found the leucocytosis during labor will average 18,000, but may reach the high of 32,000. Vogt reported a progressive increase in the blood sedimentation rate during pregnancy reaching between 23 and 32 millimeters per hour in the ninth month, and followed by a very gradual return to the upper normal limits approximately 6 weeks postpartum. Yet, Titus warns that the finding of a rapid blood sedimentation rate indicates infection, and in a pregnant woman this is a particularly serious matter. He feels that it is safer, therefore, to operate early in the presence of marked acceleration of the blood sedimentation rate.

During the first trimester of pregnancy, the most common complications involving differential diagnosis with acute appendicitis are ectopic fallopian tubal pregnancy, salpingitis, early abortion, tumors of the right ovary; during the second trimester there are added right-sided nephritis, hydronephrosis, pyelitis, hydroureter, nephrolithiasis or ureterolithiasis, mesenteric lymphadenitis, mesenteric thrombi, intestinal obstruction, ileus, duodenal and gastric ulcers, cholecystitis, and cholelithiasis. During the last trimester, additional consideration must be given to premature labor, placenta previa, abruptio placentae, eclampsia, and the complications of the toxemias. In the puerperium, it is difficult to differentiate between the expected "after-pains," parametritis, subinvolution of the uterus, cystitis, pyelitis, and the signs of acute appendicitis. Generally speaking, the differential diagnosis between acute appendicitis and uterine fibroids, as well as "red" degeneration of the uterine fibroids presents little or no difficulty.

McDonald reports an incidence of abortion in those cases of pregnancy complicated by appendicitis as follows: If the disease be limited to the appendix, the rate is 11.4 per cent; if an abscess be formed, the rate is 66 per cent; and in the presence of generalized peritonitis, the rate is 72 per cent. Jerlov, reporting on cases in Scandinavian hospitals, found the rate to be 13.8 per cent in the intrinsic disease, 55 per cent if an abscess had formed, and 63 per cent in the presence of generalized peritonitis.

McDonald reports a maternal mortality rate of 0.71 per cent when disease is limited to the appendix, 23.5 per cent when an abscess is present, and 30 per cent when peritonitis develops. The maternal mortality rates are the highest in patients who abort. Stoeckel and Greenhill have estimated this mortality rate

at approximately 25 per cent during the last trimester of pregnancy, labor and the puerperium. After rupture of the appendix, the maternal mortality rate is quoted by most authors at 50 per cent. Greenhill notes that 50 per cent of the patients abort following perforation of the appendix, and this increases the maternal mortality rate by 5 per cent. Maes and Boyce both emphasize that patients abort because they are dying; they do not die because they have aborted. Irving reported the maternal mortality rate at Boston Lying-In Hospital as 11.8 per cent, and stated that 23.5 per cent either abort or have premature labor following appendectomy.

During the first 7 months of pregnancy, early diagnosis and immediate appendectomy are considered the optimum in the surgical treatment of this problem. The uterus should be manipulated as little as possible during operation, and postoperatively every effort should be exerted to prevent premature labor and abortion.

The therapy, treatment, and type of surgical and obstetrical procedure during the last trimester of pregnancy and labor have been the subject of considerable divergence of opinion. For this reason, several of the proposed methods of surgical and obstetrical treatment of this problem as well as the date of publication are presented, so that a fair evaluation may be made in the light of the most recent advancements in surgical procedures, postoperative care, chemotherapy and antibiotic therapy.

Mundé in 1894, stated: "I would open the 'abscess' at once, as soon as a reasonable probability of its existence could be settled, without reference to the pregnancy, or the impending or complete delivery. I would prefer to take chances of puerperal infection from the abscess than of its unexpected rupture at any moment into the peritoneal cavity."

Cocke and Mason in 1920, said "If appendicitis occurs in the last month of pregnancy, termination of the labor and the removal of the appendix are indicated. If the patient is a primipara, or if there is any doubt about immediate delivery in the multipara, cesarean section followed by appendectomy should be performed."

Wilson in 1927 stated, "If perforation and peritonitis are not present, then remove the appendix and leave the pregnancy alone . . . in the presence of marked peritonitis, a rapid Porro section is the safest procedure, and the low transverse section ranks next in safety; the classical section will not yield good results when performed in the presence of severe infection. To prevent the development of fetal toxicity, the displacement of surgical drains, the tearing of adhesions, and the spread of peritonitis during labor, cesarean section followed by appendectomy is advocated as the procedure which will give the best results."

McDonald, in 1929, in a multipara at term and in labor manually dilated the cervix under ethylene anesthetic, performed a podalic version and extraction, and then a laparotomy and appendectomy. Mother and child lived. He states: "Cesarean section for cause other than obstetric should be avoided if a more conservative method of delivery is available."

Stander in 1936, said: "It is suggested that the uterus be emptied by cesarean section before attacking the appendix. We, however, do not believe that this is always necessary, and are convinced that its general adoption will add to the gravity of the operation."

Cosgrove in 1938, stated: "Acute appendicitis is a surgical condition calling for prompt operative intervention. Its surgical treatment should not be combined with any manipulation to terminate pregnancy. This statement may be modified only by the legitimacy of a simple procedure to expedite termination of the second stage of spontaneous labor, and in the case of the recognition of the very rare possibility of concurrent serious factors of obstetrical dystocia . . . such interference should be reserved until after the onset of spontaneous labor and then an extraperitoneal approach selected."

Zander in 1942, said: "The pregnant woman with acute appendicitis is first a surgical problem and second an obstetrical problem. Operation should be carried out without delay and delivery accomplished by natural channels at term unless an absolute indication is present demanding abdominal section. Porro section may be necessary if perforation or abscess formation has occurred."

TABLE I.—SUMMARY OF 26 CASES

	Hospital No.	Age	Parity	Gestation	WBC	Pathology report	Mortality	
							Mother	Child
1	194–173	32 yrs.	1	7 wks.	11,500	Acute diffuse appendicitis	No	Abortion on 4th post-operative day
2	223–201	21 yrs.	2	6 wks.	18,400	Acute periappendicitis	No	Abortion
3	221–393	30 yrs.	2	7 wks.	11,000	Acute catarrhal appendicitis	No	Abortion
4	191–720	25 yrs.	1	2 mos.	20,000	Acute catarrhal appendicitis	No	Abortion
5	160–455	29 yrs.	2	2 mos.	21,600	Subacute appendicitis	No	Abortion on 19th post-operative day
6	165–252	22 yrs.	2	2 mos.	6,750	Chronic appendicitis	No	No
7	178–574	27 yrs.	1	2 mos.	10,150	Fibrous obliteration of appendix; chronic granulomatous mesenteric lymphadenitis	No	No
8	211–972	21 yrs.	1	2 mos.	11,450	Acute appendicitis	No	No
9	219–063	22 yrs.	1	2 mos.	19,300	Acute appendicitis	No	No
10	161–168	20 yrs.	3	2½ mos.	17,600	Acute appendicitis	No	No
11	248–451	28 yrs.	2	3 mos.	16,850	Acute appendicitis (suppurative) with fecalith	No	No
12	195–752	29 yrs.	2	3 mos.	16,700	Acute suppurative appendicitis	No	No
13	211–111	25 yrs.	1	3 mos.	20,600	Acute suppurative appendicitis	No	No
14	144–900	33 yrs.	5	3 mos.	16,500	Acute suppurative appendicitis	No	No
15	258–085	22 yrs.	2	3½ mos.	18,450	Acute suppurative appendicitis	No	No
16	174–287	22 yrs.	1	4 mos.	15,000	Fibrous involution of appendix	No	No
17	170–100	24 yrs.	1	4 mos.	8,700	Fibrous obliteration of tip of appendix	No	No
18	164–086	38 yrs.	3	4 mos.	13,700	Acute appendicitis with fecalith	No	No
19	247–493	25 yrs.	1	5 mos.	11,450	Acute catarrhal appendicitis	No	No
20	218–087	34 yrs.	5	5 mos.	25,800	Acute and chronic granulomatous inflammation of large bowl consistent with clinical diagnoses of periappendiceal abscess (2 yrs. p.o. patient was operated on for partial intestinal obstruction which proved to be caused by a large mucinous adenocarcinoma of the cecum)	No	Spontaneous delivery of macerated fetus on 16th postoperative day
21	183–485	24 yrs.	2	6 mos.	6,100	Acute diffuse appendicitis	No	No
22	161–289	38 yrs.	9	6½ mos.	17,000	Acute suppurative appendicitis	Died on 3rd post-operative day	Spontaneous delivery of a stillborn on 2nd postop-erative day
23	197–456	34 yrs.	1	7 mos.	27,000	Acute gangrenous appendicitis with rupture	No	Spontaneous delivery of living female on 1st post-operative day. Wt. 885 gms., died 4 hrs. af-ter delivery
24	203–909	32 yrs.	3	9 mos.	15,000	Acute suppurative appendicitis	Died on 42nd post-operative day	Spontaneous delivery living male child. Wt. 3060 gms., died 7 mos. of age
25	71–232	27 yrs.	2	9 mos.	22,500	Acute suppurative appendicitis	No	Cesarean de-livery of living male child. Wt. 3120 gms.
26	254–243	32 yrs.	2	Puerperium	12,500	Appendiceal abscess, retroperitoneal	No	Spontaneous delivery living female child

Case 22. Thirty hours postoperatively, patient went into labor; within 1 hour spontaneous delivery of stillborn. Retained placenta with postpartum hemorrhage.

Case. 24. Labor developed postoperatively, and within 12 hours premature separation of the placenta, followed by aspiration pneumonia developed during anesthetic.

Case 25. Patient entered the hospital in labor. Transverse laparotrachelotomy type of cesarean section.

Case 26. Symptoms of acute appendicitis and rupture developed 6 hours postpartum. Appendiceal abscess drained on 2d postpartum day.

TABLE II.—SUMMATION OF APPENDECTOMIES AND DELIVERIES AT THE UNIVERSITY HOSPITALS OF CLEVELAND, 1934–1946 INCLUSIVE

Total number of deliveries	49,681
Hospital deliveries, private and staff	32,968
Home deliveries	16,713
Total number of appendectomies	10,752
Number of appendectomies performed on females between the ages of 12 and 50 years	4,330
Total number of acute appendicitis cases	2,434
Number of acute appendicitis cases in females between the ages of 12 and 50 years	822
Total number of acute appendices with rupture	415
Number of acute appendices with rupture in females between the ages of 12 and 50 years	68
Total number of appendiceal abscesses	176
Number of appendiceal abscesses in females between the ages of 12 and 50 years	38

W. Stoeckel in 1943, stated: "In the presence of peritonitis or possible abscess, the uterus must be emptied, the method of choice is for one operator to perform the appendectomy and a second operator to perform a vaginal hysterotomy; following the emptying of the uterus the surgical drains can be placed in the abdominal incision and the latter closed and then the vagina repaired."

Greenhill in 1945, said: "In consideration of the high mortality of suppurative peritonitis at or near term, perhaps it is best in the interests of the two individuals, to do an appendectomy followed by a Porro section . . . the classic cesarean section is contraindicated, laparotrachelotomy is safer, but the extraperitoneal section is still better."

Te Linde in 1946, said: "When dealing with an acutely inflamed appendix during pregnancy, regardless of stage, the removal of the appendix with the least possible amount of surgery is the safest, and the chances for spread of the infection are minimized. When there is evidence of peritonitis, five grams of sulfanilamide may be profitably left in the peritoneal cavity."

For the purpose of studying further this complex surgery and obstetrical problem, the records of the obstetrical, gynecological, and surgical services of the University Hospitals of Cleveland were reviewed for the 13 year period, 1934 to 1946 inclusive. Inasmuch as the obstetrical service maintains an "in the home delivery service" as a part of the out patient service in connection with the department of obstetrics of the Western Reserve University School of Medicine, the home deliveries are included for this same period of time. It is the practice of this service to admit to either The University Hospitals or The Cleveland City Hospital all patients developing complications requiring hospitalization during the pregnancy, labor, or puerperium. Hence, the records of Cleveland City Hospital were reviewed to assure no mistake in our series. No cases of appendicitis complicating pregnancy, labor, or the puerperium which had been referred from the district home delivery service could be found in their records.

TABLE III.—SUMMATION OF ABDOMINAL DISEASE COMPLICATIONS OF PREGNANCY, LABOR AND THE PUERPERIUM—THE UNIVERSITY HOSPITALS OF CLEVELAND 1934–1946 INCLUSIVE

Disease	Number of cases
Acute appendicitis	26
Ectopic fallopian tubal pregnancy	158
Ovarian tumors or cysts	46
Cholecystitis	16
Acute salpingitis	9
Hydronephrosis	1
Urolithiasis	2

Table I, presents in brief, a summary of 26 cases of appendicitis complicating pregnancy, labor, or the puerperium which have occurred in this 13 year period at The University Hospitals of Cleveland. Cases 22 and 24 are illustrative of the fatal type of postoperative complications which may develop during labor and delivery following appendectomy. The high leucocytosis range in almost every case is of particular interest. Cases 7 and 20 bespeak of the more rare complications which may be encountered. In this series, 84.6 per cent of the patients developed acute appendicitis during the first 6 months of gestation. The abortion rate was 26.1 per cent, the fetal and neonatal mortality rate (including abortions) was 34.6 per cent, and the maternal mortality rate 7.69 per cent.

Table II presents a summation of the total number of deliveries and the total number of appendectomies during this same 13 year period at the University Hospitals of Cleveland. In this 13 year period, there was an incident rate of appendicitis complicating pregnancy, labor or the puerperium of 1 to 1,910

deliveries. An incident rate of pregnancy associated with acute appendicitis in females within the childbearing age of 1 to 31, was found.

Table III presents a summation of the abdominal disease complications of pregnancy which required hospitalization or surgery during this same 13 year period at The University Hospitals of Cleveland. Uterine fibroids have been omitted because it was not considered that they produce a syndrome which might readily be confused with acute appendicitis.

Table IV is a review of a large number of the reported cases found in literature. Jerlov's series is omitted because it is understood to be included in Heineck's series. We make no apologies for the completeness of this series, for the problem of reviewing medical literature on this subject is one of considerable proportions. This series is presented primarily to emphasize the rarity in which acute appendicitis occurs as a complication of labor or the puerperium.

Within the past several months, 1 case with appendicitis complicating term labor, and 1 case with appendicitis complicating the puerperium, have been seen on the Obstetrical Service of University Hospitals of Cleveland. They are cases 25 and 26 in Table I. In discussing these 2 cases with our Cleveland colleagues, it was learned that 2 cases of acute appendicitis complicating the puerperium had been seen during the past year at St. Ann's Maternity Hospital of Cleveland. Through the courtesy of Dr. Edward J. Keefe and the late Dr. Ralph B. Thompson, the clinical histories of these 2 cases as well as the clinical histories of the 2 cases from our own service are presented.

TABLE IV.—COLLECTION FROM MEDICAL LITERATURE OF REPORTED CASES OF APPENDICITIS COMPLICATING PREGNANCY, LABOR AND THE PUERPERIUM

Author	Cases	Cases in labor	Cases in puerperium
Schmid	486	0	0
Heineck	405	2	0
Abrahams	11	4	0
D'Erricco	65	0	0
Maes	50	0	0
McDonald	33	0	0
Baer, Reis, Arens	28	0	0
Wilson	10	0	1
Finley	9	0	0
Portes Seguy	7	0	0
Puppel	6	1	0
Fullerton	14	0	0
Cosgrove	28	2	0
Garcia	94	0	0
Smith and Bartlett	20	0	0
Guerriers	16	0	0
Barber and Miller	0	1	0
Gratten	0	1	0
King	0	1	0
Krauss	0	1	0
Le Jemetel	0	1	0
Rose	0	1	0
Hilton	0	0	30

CASE 1 (Case 25 in Table I). B. Z., Hosp. No. 71-232. Private patient of Dr. Folger.

The patient was a 27 year old white female, secundipara, admitted to the Obstetrical Service of University Hospitals on September 5, 1946. She was first seen by the attending obstetrician during the third month of gestation. At this time, the hemoglobin was 50 per cent; blood pressure, 100/30; serology, negative. Pelvic measurements were within normal limits. Previous labor was normal, and the child weighed 6 pounds, 14 ounces at birth. Present antenatal course was uneventful until the sixth month of gestation at which time she had one episode of acute lower abdominal pain. Bed rest and sulfadiazine therapy resulted in complete recovery. Thirty-six hours prior to admission, patient had sudden recurrence of lower abdominal pain radiating to the lumbar region and associated with nausea and vomiting. Sedation relieved these symptoms. On admission to the hospital, this patient was apprehensive and in apparent acute distress. She complained of severe abdominal pain accompanied by nausea and vomiting of less than 2 hours' duration. Examination revealed no abnormalities of the cardiovascular or respiratory systems. The abdomen protruded with the tumor of pregnancy extending to 8 centimeters below the xiphoid process. The anterior abdominal wall was tense and tender to palpation. The rectus muscles were not rigid. There were irregular uterine contractions lasting 50 seconds and occurring at intervals of 3 to 6 minutes. Rectal examination revealed the cervix to be patulous, and dilated from 1.5 to 2 centimeters. No acute tenderness was noted on tensing the rectal walls. There was no vaginal discharge. The renal areas were nega-

tive. Hemoglobin was 88 per cent; white blood cells, 22,650; urine, essentially negative; temperature, 38 degrees; blood pressure, 100/50; pulse, 100; respirations, 24; fetal heart rate, 140 in right lower quadrant. Following sedation with demerol, 100 milligrams intramuscularly, patient received some relief. During the next 6 hours she was observed. The uterus remained tense, the abdominal pain was more pronounced on the left lateral wall, but the entire abdomen was acutely tender to all palpation. Consultation was held, and a tentative diagnosis of placental separation with retroplacental hematoma and intrauterine hemorrhage was made. A secondary diagnosis of twisted, gangrenous, ovarian cyst was considered. The fetal heart at this time was very rapid. Cesarean section was immediately performed.

When the abdomen was opened through a low midline incision, purulent exudate was encountered. Transverse laparotrachelotomy was performed. A living, female infant weighing 3120 grams was delivered. The placenta and membranes were not remarkable. The myometrium was closed in layers. The uterovesical peritoneal fold was imbricated and advanced 3 centimeters in covering the uterine incision. The uterus was then delivered through the abdominal incision. Appendectomy was performed and the stump was ligated but not inverted. Ten grams of sulfathiazole crystals were placed in the peritoneal cavity. The abdominal wall was then closed in layers and the skin was closed with clips.

Postoperatively, the patient was given 100,000 units of penicillin intramuscularly every 4 hours for 7 doses following which she received 20 doses of 50,000 units each intramuscularly, a total of 1,700,000 units of penicillin. A Levine tube was passed into the stomach immediately after operation, and gastric suction was maintained for 72 hours. She received 250 cubic centimeters of whole blood, following which she had a mild thermal type reaction. Glucose and saline intravenous solutions were given for 48 hours. On the third postoperative day she was afebrile and was given a liquid diet. On the fourth postoperative day she was given a soft diet followed by a regular house diet. She remained afebrile. On the fifth postoperative day the white blood count was 20,500. The patient was discharged on the tenth postoperative day; both she and the baby were in good condition. Pathologist's report: "Acute suppurative appendicitis."

CASE 2 (Case 26 in Table I). M. B., Hosp. No. 254-243 Staff Service.

The patient was a 32 year old white female, secundipara, admitted to the Surgical Service of University Hospitals June 9, 1946. She was not attended by a physician during her antenatal course of during labor. Following delivery of a living, female child weighing 7 pounds, 8 ounces, she requested medical attention. The externe answering this request expressed the placenta and membranes without difficulty. She was given ergotrate, 1/320 grain, by mouth. Temperature was 37.4 degrees; blood pressure, 110/65; pulse, 98. Labor was estimated at 10 hours according to the patient's story. It was not remarkable. For afterpains, the patient received 4 doses of paregoric, 1 teaspoonful at 3 hour intervals.

Approximately 6 hours postpartum, the patient experienced shaking chills accompanied by sharp pain in the right flank radiating to the right costovertebral angle. The patient was visited at this time by one of the obstetrical residents. Temperature was 39.5 degrees; examination revealed diminished breath sounds over the right chest. The abdomen was markedly distended, no rebound tenderness; there was a visible bulging of the right abdominal wall over the crest of the ileum. The patient was sent immediately to the hospital and admitted on the Surgical Service with a tentative primary diagnosis of paranephric abscess on the right, and a secondary diagnosis of possible acute appendicitis with perforation and peritonitis.

Hemoglobin was 80 per cent; white blood cells, 12,500. The urine showed traces of albumen, with 10 to 15 red blood corpuscles per highpowered field, and 5 to 10 white blood cells per highpowered field. X-ray film of the chest was negative. Retrograde pyelograms revealed moderate hydronephrosis and dilatation of the right ureter. She was observed for 30 hours, following which she was taken to surgery and a retroperitoneal abscess of the right lateral abdominal wall drained of 500 cubic centimeters of thick, purulent exudate. The abscess cavity was irrigated with normal saline, and at its base the cecum and the edematous appendix could be visualized. The peritoneum was not entered. The cavity was loosely packed, and a large cigarette drain was inserted. Postoperatively she received intravenous sulfadiazine and 30,000 units of penicillin intramuscularly every 3 hours. After the first day, sulfadiazine therapy was given by mouth. The sulfadiazine therapy was continued until her eighth postoperative day, and the penicillin until her twelfth postoperative day. Hot abdominal stupes were used for 10 days.

The temperature ranged from 39.5 degrees the first 24 hours postoperatively to 37.5 degrees on the sixth postoperative day. She remained afebrile the remainder of her hospital stay. Sulfadiazine level on the first postoperative day was 10.4 milligrams and on the eighth postoperative day 2.4 milligrams. Blood urea nitrogen on the second postoperative day was 19.5; blood chlorides, 98.8; serum protein, 6.5; urine culture showed hemolytic Staphylococcus albus; abscess culture showed Bacillus coli, Staphylococcus aerogenes.

The patient was ambulatory on the seventeenth postoperative day and discharged on the twenty-first postoperative day. Two months after operation the abscess wound was completely granulated and there was no drainage. She was advised to return in 4 months for an elective appendectomy. Roentgenogram showed marked reduction in the size of the right hydronephrosis.

CASE 3. G. C. Hosp. No. C-898. Staff patient at St. Ann's Maternity Hospital.

This patient was a 31 year old white female, quadripara, admitted to St. Ann's Maternity Hospital July 23, 1946. Previous pregnancies and labors were uncomplicated; three living children. She attended the obstetrical out patient department at St. Ann's Hospital beginning in the fourth month of this gestation. During the sixth month of pregnancy, she was admitted to the hospital complaining of vague right upper quadrant abdominal pain; no nausea or vomiting; no temperature elevation. Following 36 hours of bed rest patient was discharged. The patient entered the hospital at term, with labor well established. Physical examination was essentially negative. She received demerol and scopolamine analgesia during the first stage of labor which lasted 8 hours and 15 minutes. Second stage was of 55 minutes' duration. Patient was given nitrous oxide oxygen and ether and delivery was by means of outlet forceps. Placenta and membranes were delivered complete. Third stage duration was 5 minutes. Patient received ergotrate 1/320 grain intravenously and then three times a day for 2 days. On the first postpartum day, the patient developed abdominal distention, with temperature elevation of 38 degrees. She complained of generalized abdominal pain. The white blood cells numbered 15,900. Hemoglobin was 80 per cent. Enema was given with no return. Later in the day, there was one semimucous bowel movement. On the second day she developed nausea and vomiting, continued abdominal distention, and temperature of 39.3 degrees. She was expelling flatus and passing loose stools. Enema was given but brought no return. One ampul of prostigmine was given every 4 hours for 6 doses; rectal tube *ad libitum;* penicillin, 100,000 units initially, followed by 30,000 units every 3 hours, 4 times. Intravenous fluids were administered. On third postpartum day gastric suction was started. Penicillin and prostigmine were continued. Two enemas were given, with good results. The white blood count was 8,700; temperature dropped to 38.2 degrees. Fourth postpartum day abdomen was soft. Gastric suction and penicillin therapy were discontinued; no vomiting; liquid stool. Tenderness was present over the left lower quadrant and umbilicus. During the night of this day abdominal distention developed with pain in the right lower quadrant and epigastrium. Gastric suction was started again. On the morning of the fifth day, the patient had a chill; skin became cold and clammy; pulse, 130; blood pressure, 90/55; temperature, 40.1. Penicillin was restarted at 50,000 units intramuscularly every 3 hours. White blood cells numbered 11,900. Blood plasma and intravenous glucose were given. Patient lapsed into unconsciousness and her condition became progressively worse, her temperature reaching 42 degrees. She died approximately 18 hours after shock had first occurred.

Pathologist's report—autopsy findings: acute gangrenous inflammation of the appendix with perforation and fecalith; acute diffuse nephrosis; diffuse acute fibrinopurulent peritonitis (1000 c.c.); cloudy swelling of the liver and adrenals; corpus luteum cyst of left ovary; acute inflammation and necrosis of decidua; acute hypertrophy of the uterus (recent pregnancy); acute hyperplasia of the spleen.

CASE 4. K. F. Hosp. No. 45-8309, Huron Road Hospital, private patient of Dr. E. J. Keefe.

This was a 23 year old white primipara. First prenatal visit was in the second month of gestation. She had a uniformly contracted pelvis—bispinal diameter 21 centimeters; bicrestal, 26.5 centimeters, external conjugate, 18, diagonal conjugate, 10.5 centimeters; blood pressure 110/70; urinalysis, essentially negative; serology, negative. Physical examination revealed nothing remarkable. Antenatal course complicated by nausea and vomiting during the first 6 months of pregnancy was relieved by vitamin B therapy and sedation. X-ray pelvimetry during the fortieth week of gestation revealed marked cephalopelvic disproportion with the fetal head not engaged. Elective cesarean section was performed at St. Ann's Maternity Hospital on October 4, 1945. Low cervical type under nitrous oxide oxygen and ether anesthesia. The uterus was closed in layers, also the abdomen. A living, male child was delivered. Placenta and membranes were removed complete. The postoperative course was without incidence until the eighth postoperative day. At this time the patient noted general epigastric discomfort, nausea, but no vomiting. Temperature elevation was 38.2 degrees. No relief came from an enema and the use of sedation. On the ninth postpartum day there was slight abdominal distention; abdominal pain was localized in the right lower quadrant, with marked rebound tenderness. Temperature was 38.5 to 38.7 degrees. Rectal examination revealed extreme tenderness in the right iliac fossa. Uterus was well involuted, lochia, normal. The abdominal wound was healing by first intention, with no drainage and no tenderness (sutures were removed on the seventh postpartum day). White blood cells numbered 18,000 to 20,000; urine was negative. A diagnosis was made of acute appendicitis, and the patient was transferred to the surgical service of Huron Road Hospital. Laparotomy was immediately performed under spinal anesthesia and cyclopropane. When the abdomen was opened through a right rectus incision, profuse, thin, purulent exudate was encountered. The appendix was inflamed and swollen, covered by fibrinous exudate, and located retroperitoneally. Appendectomy was performed; the stump was not inverted. Ten grams of sulfathiazole crystals were distributed in the peritoneal cavity. The uterine incision was walled off by the omentum, and this was not disturbed. One large cigarette type drain was placed at the base of the cecum, and the abdomen was closed in layers. After operation the patient received 500 cubic centimeters of whole blood, 20,000 units of penicillin every 3 hours for 4 days, and continuous hot abdominal stupes for 4 days. After the first post-

operative day she was afebrile. The drain was removed on the fourth postoperative day. Sutures were removed on the seventh postoperative day, and the patient was ambulatory on her eighth postoperative day. She was discharged on the ninth postoperative day. Pathologist's report: "Acute suppurative appendicitis."

It is indeed a coincidence that these 4 cases of this serious surgical and obstetrical problem occurred here in Cleveland within the past year. Each case presents a different phase of the masked diagnostic clinical signs and symptoms. These 4 case histories warrant presentation if for no other reason than to emphasize the great difficulty encountered in making an early, correct diagnosis of acute appendicitis. Case history 3 reveals the serious consequences of the delayed diagnosis, followed by inadequate chemotherapy or antibiotic treatment, and insufficient gastrointestinal decompression. The use of enemas and prostigmine must be attributed to the incorrect diagnosis. Cases 1, 3, and 4 present the satisfactory results following correct, early diagnosis, properly executed surgical procedures, adequate intravenous nutrition, maintenance of gastrointestinal decompression, and sufficiently prolonged administration of chemotherapy and antibiotic therapy.

DISCUSSION

If this complicated surgical and obstetrical problem is considered as a pathological condition involving the appendix and a physiological condition involving the pregnancy, then it behooves us to find the best remedy to obliterate the pathological condition. One is impressed by the geometrical rise in the mortality rates to both mother and child in the presence of peritonitis.

The optimum of treatment during the first 7½ months of pregnancy is as stated above, a well timed and properly executed appendectomy, with the least possible manipulation of the uterus, gastrointestinal decompression, blood, plasma, and fluids intravenously, and adequate chemotherapy and antibiotic therapy. Postoperatively, some authors report good results from the intravenous administration of estrogen-progesterone therapy to avoid abortion or premature labor.

The difficult problem, then, occurs in the treatment of the patient during the last 2½ months of pregnancy, labor and the puerperium, particularly if perforation of the appendix has taken place followed by diffuse peritonitis.

Meyer, Requarth, and Kozoll found that the lowered mortality rate at Cook County Hospital for acute appendicitis with perforation and peritonitis is chiefly attributed to the use of chemotherapy. They have demonstrated that this rate was reduced from 26.4 per cent (1928–1938) to 13.9 per cent (1944–1945). These same authors report that appendectomy with drainage is associated with the highest mortality rates. Hoerr, in reviewing the fatalities in operative appendicitis between 1913 and 1940 at the Peter Bent Brigham Hospital, found delay in operation the major factor in cause of mortality. He also states that closure without drainage is vindicated in his study. Waugh, McCall, and Herrell at the Mayo Clinic found no marked difference in the relative efficacy of sulfanilamide and sulfathiazole used intraperitoneally in perforated appendicitis. They state that following implantation of either sulfanilamide or sulfathiazole intraperitoneally, supplemental intravenous, oral or subcutaneous chemotherapy should not be started until after the second or third postoperative day, and then may be continued for 5 days or longer if necessary. It is of note that they found high concentrations of sulfanilamide (ranging from 22 mgm. to 1,330 mgm. per 100 c.c. of peritoneal fluid) persisted at the site of the deposit in the peritoneal cavity for longer than 24 hours. They reported that the intraperitoneal use of sulfathiazole and sulfanilamide was the chief factor in reducing the mortality rate of perforating appendicitis from 16.9 to 3.8 per cent at the Mayo Clinic between 1936 and 1942.

Crile's recent report of 50 patients with proved appendiceal peritonitis successfully treated by the administration of 100,000 units of penicillin at 2 hour intervals for several days, commends the use of these large doses of penicillin in the presence of peritonitis. (He suggests that the large doses of penicillin are necessary to combat the action of the Escheri-

chia coli, which is known to have an inactivating effect on penicillin.)

Woltz and Zintel found no evidence of penicillin toxicity to either mother or child when penicillin was administered to the pregnant patient. Adequate penicillin levels were produced in both maternal and fetal circulation and in the amniotic fluid. Eastman, in commenting on this study, suggests the value of penicillin therapy in treating intrapartum infection and as a prophylaxis against intrauterine infection.

Tenney, in commenting on the causes of maternal deaths in obstetrics, reports that sepsis still continues in 1946 to be one of the most important causes. He states that the treatment of sepsis resolves itself into the primary factors of blood transfusions, fluids, nutrition, rest, and chemo-antibiotic therapy.

How similar this recommendation is to 4 major contributions in the field of surgery of the past 2 decades which are applicable in the modern treatment of acute appendicitis and peritonitis: (1) gastrointestinal decompression, (2) intravenous nutrition, (3) plasma and whole blood transfusions, (4) chemotherapy and antibiotic therapy.

The small number of cases reported in this paper warrants conservatism in recommending the method of choice in treating this surgical and obstetrical complication. It is to be recalled that acute appendicitis complicating the last trimester of pregnancy, labor, and the puerperium is rare; hence anyone observer is hardly justified in generalizations with regard to therapy. The existence of the promising new therapeutic weapons of chemotherapy and antibiotic agents must not blind us to the importance of the many other factors involved in the proper care of the patient with acute appendicitis. In the hope of diminishing the maternal and infant (toxic) complications, and maternal and fetal mortality rates, the following suggested treatment warrants consideration by obstetricians, gynecologists, and surgeons confronted with a patient with acute appendicitis, with or without perforation, complicating the last 2 months of pregnancy or labor: Cesarean section by low transverse laparotrachelotomy, followed by properly executed appendectomy, intraperitoneal implantation of 5 to 10 grams of sulfanilamide or sulfathiazole crystals, massive doses of penicillin postoperatively for several days accompanied by gastrointestinal decompression, blood and plasma transfusions, and intravenous nutrition. It is to be remembered that appendectomy is performed not to treat appendicitis, but to prevent peritonitis. Cesarean section in these cases provided the maximum opportunity for both mother and child to survive what may otherwise prove to be fatal postoperative complications, such as adhesions, disrupted surgical incisions, and intestinal obstructions with their accompanying peritonitis.

SUMMARY

1. A brief summary is presented keynoting the problem involved in making the diagnosis of acute appendicitis complicating pregnancy, labor, and puerperium.

2. A 13 year (1934–1946 inclusive) statistical summary of the records of the obstetrical, gynecological, and surgical services of University Hospitals of Cleveland, showing the incidence of abdominal disease complications of pregnancy, is presented in 3 tables. A fourth table presents the work of other authors in statistical form to emphasize the rarity of acute appendicitis complicating labor or the puerperium.

3. Four case histories of patients with acute appendicitis complicating labor or the puerperium which occurred in Cleveland during 1945 to 1946 are presented.

4. The efficacy of the use of chemotherapy and antibiotic therapy in the treatment of appendicitis and peritonitis is discussed.

5. No absolute conclusion is presented as to the optimum in the surgical and obstetrical treatment of the patient presenting acute appendicitis as a complication of pregnancy, labor, or the puerperium. The method which was followed in our recent cases, when combined with the experience of others, in the use of the modern methods of surgery and postoperative therapy and care, may serve as a basis to reduce the maternal and fetal complications, and to decrease the maternal, fetal, and neonatal mortality rates in this serious surgical and obstetrical problem.

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PROGRESS IN THE SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID COLON

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SINCE the turn of the century, when the clinical significance of diverticula of the colon first came into prominence through the writings of Graser, Fischer, Beer, Mayo, Wilson and Giffin, Moynihan, Telling and others, many valuable contributions to knowledge of the subject have been made by a host of workers (2, 6, 8, 11, 14, 16, 20, 22–24, 26). The literature is now voluminous, dealing with nearly every phase of the subject, such as the incidence, etiology, and recognition of diverticulosis and the symptomatology, classification, recognition, and management of the secondary pathologic changes; that is, diverticulitis and its sequelae. Knowledge derived from these studies is widespread, so that the value of further discussion of the subject would appear to be limited to emphasis and appraisal of established facts were it not that in recent years surgery of the colon has made momentous progress. In view of these advances, re-evaluation of the surgical management of diverticulitis of the sigmoid seems definitely indicated to determine if the practice and teachings of former years are still valid.

Surgery in the management of diverticulitis is limited largely to the treatment of certain complications, notably perforation, obstruction, and fistula. Brown wrote, "There should be a determined effort to avoid operation," but he pointed out that it was both futile and dangerous to persist in a medical regimen after development of the complications just mentioned. In addition to these classical indications for operation, it is frequently impossible to exclude carcinoma on clinical grounds, and exploration for this reason often is justified. There is lack of agreement as to what should be done surgically in the management of complicated diverticulitis, particularly as to the necessity of resection in many cases. Since the literature contains no report of a series of cases of diverticulitis in which surgical treatment has been carried out in conjunction with modern chemotherapy, the present study, therefore, was undertaken with a twofold purpose in mind: (1) to appraise the different surgical procedures in the management of diverticulitis of the sigmoid, and (2) to determine what effect the application of modern chemotherapy has had on the immediate mortality.

Records were available of 389 patients[1] whose diverticulitis involved the sigmoid only, or the sigmoid together with a portion of the descending colon, and who were treated surgically. For the purpose of this study, the patients were divided into two series: namely, series A, which comprised 245 patients treated surgically in the years 1908 to 1940 inclusive, and series B, which comprised 144 patients operated on in the years 1941 to 1945 inclusive. The data relating to incidence and symptomatology of the disease cited were derived from the records of the latter series (B), whereas the data relating to late results of treatment were obtained, primarily, from the earlier series (A). The surgical mortality rate of each series was computed.

It is estimated that in excess of 5 per cent of all individuals more than 40 years of age have diverticulosis of the colon but the condition is rare among persons less than this age. Of more than 47,000 roentgenologic examinations of the colon made at the Mayo Clinic in the pe-

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[1]Patients whose diverticulitis was discovered at operation directed primarily at treatment of some other lesion, and who were not treated surgically for the diverticulitis, were not included in this series. Five patients have been included two times in this series. In each case, the patients were treated surgically for diverticulitis, the disease recurred and another series of operations was carried out. There were actually 384 individuals in the series.

TABLE I.—SYMPTOMS AND SIGNS OF DIVERTICULITIS OF SIGMOID IN 144 CASES IN WHICH OPERATIONS WERE PERFORMED—SERIES B

Symptoms or signs		Cases	Per cent of 144*
Evidence of inflammation		114	79
Complete or partial intestinal obstruction		43	30
Diarrhea		27	19
Mucus in feces		9	6
Blood in stool		12	8
Mass		52	36
Abdominal	21		
Pelvic	31		
Fistula		61	42
Sigmoidal cutaneous	23		
Sigmoidovesical	22		
Sigmoidoenteric	4		
Multiple	7		
Other types	5		

*More than one symptom or sign encountered in each of many cases.

riod 1941 to 1945 inclusive, diverticulosis was discovered in 8.5 per cent. It is not known in what proportion of patients with diverticulosis symptoms attributable to inflammatory changes in the diverticula will develop but Abell has estimated that 10 to 20 per cent, and Brown and Marcley that 12 to 16 per cent, of patients with diverticulosis ultimately will have diverticulitis. In the same period (1941 to 1945, inclusive) the diagnosis of diverticulitis of the sigmoid was made in 600 cases, which represent 15 per cent of the cases of diverticulosis. Of the 600 cases of diverticulitis, in 144 cases, or 24 per cent, surgical treatment was employed. Thus, it can be estimated that in about 1 out of every 4 patients with diverticulitis complications requiring surgery will develop.

The age and sex distribution of patients in series B was in keeping with those of patients reported by others. The youngest male in the series was 29 years, and the youngest female 33 years of age; the oldest male was 80 years and the oldest female 79 years of age, while the mean age was 53.6 years at the time of the operation. The ratio of males to females was 2 to 1.

Since diverticulitis may be severe from the onset of symptoms, it is not surprising that many patients required operation relatively soon after their first symptoms were noticed. In series B, 12 per cent of the patients were operated on within 1 month and 31 per cent within 6 months of the onset of the disease. It is of some interest that a greater proportion of patients in the older age groups were operated on sooner after the onset of symptoms than were the younger patients. Thus, of the patients in their forties or less, 19 per cent were operated on within 6 months of the first symptoms; of those in their fifties, 29 per cent, and of those in their sixties or more, 38 per cent.

The symptoms which the patients in series B presented are shown in Table I. Such symptoms and signs as tenderness, fever, and leucocytosis have been grouped under the broad heading of inflammation. Many patients presented several of the symptoms listed. On physical examination, 36 per cent had a mass which could be palpated beneath the abdominal wall or through the rectum and 42 per cent had a fistula which had followed former operative procedures or had developed spontaneously. Certain other signs, not covered in Table I, were significant and will be set forth here. Evidence revealed by sigmoidoscopic examination was of considerable value in the diagnosis. Of the 94 patients who were subjected to sigmoidoscopy, findings suggestive of diverticulitis, such as unusual sacculation, angulation, fixation of the bowel, constriction of the lumen, edema of the mucous membrane or the presence of an extraluminal mass were recorded concerning 63 per cent, while one or more diverticula were visualized in examination of 14 per cent. Roentgenologic examination after barium enema was of the greatest aid in the diagnosis. This procedure was carried out on 104 patients. The diagnosis of diverticulitis, diverticulosis, or both was made in 66 per cent of this group, the diagnosis of an obstructing lesion in 22 per cent, the diagnosis of an obstructing lesion of questionable malignant nature was made in 3 per cent, and the diagnosis of a fistula of the sigmoid only was made in 8 per cent. Thus, in only 1 per cent did the roentgenologic examination fail to show any evidence of a lesion suggestive of diverticulitis or diverticulosis.

It is agreed generally that carcinoma is no more likely to develop in a segment of bowel

involved by diverticulitis or diverticulosis than it is in a segment of bowel not so involved. Furthermore, the association of diverticulitis and carcinoma is not common. Rankin and Brown reported that in 227 cases of diverticulitis, carcinoma was encountered in only 4 and that diverticulitis was present in only 4 of 679 cases of carcinoma. During the period 1941 to 1945 inclusive, 11 of the patients who were successfully operated on for carcinoma of the colon or rectum were found, by the surgeon or pathologist, to be suffering also from diverticulitis of the sigmoid. In 5 cases the carcinoma was situated in a segment of bowel distant from the diverticulitis. Since the operative procedure was primarily directed toward removal of the carcinoma in all of the cases, the inflammatory lesion was considered of secondary significance and this group of 11 cases was not included in the series of cases of diverticulitis.

While there is perhaps no causal relationship between diverticulitis and carcinoma, the clinical manifestations and gross appearance at operation of these two stenosing lesions are frequently indistinguishable one from the other, as was first pointed out by Moynihan in 1907. In roughly 25 per cent of the cases in this series, carcinoma could not be excluded by clinical methods of examination. Even at operation the surgeon was unable to differentiate between carcinoma and diverticulitis in many cases. The error was made both ways and several cases of what was mistakenly considered to be locally inoperable carcinoma were proved subsequently to be cases of stenosing diverticulitis. More frequently, extensive resection was done to remove radically a supposedly malignant lesion, either without preliminary colostomy or within a few weeks after the establishment of a colonic stoma. It was thought that, for the patient's sake, sufficient time could not be allowed to elapse for the inflammatory reaction to subside. If the delay had been thought advisable, the inflammatory character of the lesion would have become evident.

SURGICAL TREATMENT OF DIVERTICULITIS

Various surgical procedures were employed to treat the patients in both series. The factors that influenced the choice of procedure employed were diverse, the most important of which were the presence or absence of obstruction, the acuteness of the process, the extent of the peridiverticulitis and of inflammation of the mesocolon, the presence or absence of fistula and the relative accessibility of the involved segment of the sigmoid. Patients treated surgically in essentially the same manner were grouped together and an attempt was made to evaluate the results following the different methods of surgical treatment, both as to the immediate mortality and the ultimate outcome. It is evident that when the involved segment of bowel is not resected, recurrence of the diverticulitis always remains a possibility.

TABLE II.—DATA ON SURGICAL PROCEDURES PERFORMED IN THE CASES IN SERIES B PRIOR TO ADMISSION TO CLINIC

Previous operations	Cases	Finding on admission	Cases
Ileostomy (2 months previously)	1	Ileostomy	1
Colostomy	12	Inadequate diversion	5
Drainage or removal of appendix	19	Abdominal fecal fistula	18
		Abdominal vesical fistula	1
Drainage; colostomy	4	Abdominal fecal fistula	2
		Abscess	1
		Cutaneous enterocolic fistula	1
Colostomy; closure	1	Cutaneous fistula	1
Drainage; attempt to close fistula	3	Cutaneous fistula	3
Colostomy; repair of sigmoidovesical fistula; closure of colonic stoma	1	Sigmoidovesical fistula	1
Cecostomy	1	Vesical fistula	1
Colostomy and repair of sigmoidovesical fistula	1	Sigmoidovesical fistula	1
Exteriorization operation	1	Persistent colostomy	1
Colostomy and resection of sigmoid	1	Persistent colostomy	1
Total	45		

The various surgical procedures to be discussed subsequently were all carried out at the Clinic. Many patients in both series had had previous operations, because of diverticulitis, before they were first seen here. Since many such operations on patients in series A were of historic interest only, they will not be mentioned. The previous operations on patients

in the more recent series B, however, reflect current practice in the more acute phases of complicated diverticulitis and have been summarized in Table II. The majority of these operations had obviously been emergency procedures, and in many cases the diagnosis had not been established before the operation. In about half of the cases an ileal, cecal, or colonic stoma had been established, and in more than half of the cases drainage, coupled with appendectomy, colostomy or closure of a fistula, had been instituted. It is evident that the operations were of necessity limited by the extent of the inflammatory process, obstruction, or other factors in the great majority of cases. The results of the previous, usually limited operations, also are listed in Table II. Such limited operations, obviously, cannot be expected to cure the patient and, in cases in which drainage of abscesses that have resulted from perforated diverticulitis is instituted, the patients should be warned of the probability of fecal fistulas and that further surgical treatment probably will be necessary to effect a cure.

Local excision of a diverticulum or of a fistula. Rarely the inflammatory reaction in a case of diverticulitis of the sigmoid is confined to a single diverticulum and the remainder of the colon is relatively unaffected, so that excision of the involved diverticulum and subsequent closure of the opening in the bowel may be considered. Similarly, either sigmoidovesical or sigmoidocutaneous fistulas occasionally may be so managed.

In series A, 17 patients were treated in this fashion with 1 death in hospital, the result of a pulmonary embolism. Of the 16 cases in which the patients survived operation, the results in 2 are not known; 9 patients have remained well and 5 are not cured. Of the 14 patients on whom the follow-up data were available 4 had had sigmoidovesical fistulas and, of these, 2 fall in the group of 9 who have remained well. Of the 2 others of this group of 4, however, 1 has a persisting fecal fistula, and the sigmoidovesical fistula of 1 recurred; these 2 patients, then, fall in the group of 5 who were not cured. The other 3 of the 5 patients who were not cured have had recurring bouts of tenderness, fever, and pain. In view of the limited inflammatory reaction which must have been present to permit satisfactory suture of the wall of the bowel, it would seem that the results following this procedure were unsatisfactory and unpredictable.

In series B, an attempt was made in 3 cases to excise a fistulous tract as a primary surgical procedure. Success was achieved in none. All 3 patients were ultimately cured by resection of the involved segment of sigmoid.

Colostomy. There is general agreement that establishment of a stoma in an uninvolved segment of colon orad to that involved by the diverticulitis will be followed by marked subsidence of the inflammatory reaction. The procedure is advocated for relief of obstruction, for treatment of perforations into the free peritoneal cavity, and in many cases as a measure preliminary to resection of the involved segment of colon.

Of 245 cases in series A, a colonic stoma was established in 117. In the majority of cases, after the colonic stoma had been established, the involved segment was resected or the stoma was closed, but in 32 cases closure was not made. Two of these 32 patients died subsequently of causes unrelated to their diverticulitis, and 3 other patients were lost track of. The remaining 27 of the 32 patients were followed for sufficient time to allow evaluation to be made of the results following diversion of the fecal stream in the treatment of complicated diverticulitis. Two patients of the 27 had sigmoidovesical fistulas and were not relieved entirely of their symptoms, while 19 patients, including 2 others who had sigmoidovesical fistulas, considered themselves well. The remaining 6 of the 27 patients continued to fail after establishment of the stoma and ultimately died, essentially of complications resulting from the diverticulitis. These 6 deaths would suggest that establishment of the stoma should not be postponed too long; in each case the death resulted from multiple pelvic abscesses and their complications, which probably could have been prevented had the fecal stream been diverted before the inflammatory process had become so extensive. In the usual case, however, establishment of the colonic stoma was followed by subsidence of most of the symptoms of the

diverticulitis and, even when a sigmoidovesical fistula existed, considerable improvement occurred as long as the fecal stream was diverted completely.

Of the 144 cases in series B, colostomy was performed in 89, either as a stage preliminary to resection or excision of a fistulous tract, or as a definitive measure of treatment. Thus, a definitely greater proportion of patients in series B (62 per cent) were subjected to colostomy than in series A (48 per cent). However, of the 89 patients of series B who underwent colostomy, only 1 died, a mortality rate of 1.1 per cent, compared with a mortality rate of 5.1 per cent in series A.

If a colonic stoma has been established, with adequate indication, for the treatment of diverticulitis, it would seem that there is no certain way to determine if the stoma can be closed without recurrence of the disease. Dixon stressed the time element and stated that closure should not be attempted for at least 12 months, while Jones expressed the belief that closure should not be attempted for from 6 to 12 months. W. J. Mayo wrote that closure could be done if the infective process had regressed spontaneously sufficiently to restore the lumen of the colon. Abell wrote that colostomy may permit such complete subsidence of the inflammatory process that the stoma can be closed; and Laufman, expressing much the same conception, wrote that if the infection did not completely subside after some months, then resection might be necessary. Judd and Phillips declared that not all patients who had colonic stomas would require resection, while Brown wrote that if a sigmoidovesical fistula was not present, the patient had about an equal chance that surgery beyond establishment of the colonic stoma would not be necessary. In our opinion, resection of the involved segment of the sigmoid should be advised in all cases before closure of the colonic stoma is attempted, unless the diverticulitis has subsided completely, as judged by clinical, proctoscopic, and roentgenologic examination and, even in such cases, the patient cannot be assured of freedom from subsequent attacks of diverticulitis. We believe that this rather radical view is supported by the results in this series of cases.

In series A, 31 patients were treated by establishment of a colonic stoma orad to the diverticulum and the stoma later was closed. Closure was not attempted before 6 months had elapsed and, in 1 case, it was postponed for 60 months. In 2 of the 31 cases, a sigmoidovesical fistula was closed in addition to establishment of the stoma. There was 1 death in hospital in the series following closure of a stoma which had been established before the patient came to the clinic. One case probably should be excluded from the series, since the diagnosis was not made with certainty before operation and since repeated roentgenograms of the colon after the stoma had been established gave negative results. Of the remaining 29 patients, 9 were well at the last report and 20 were known to have serious recurrent symptoms.

Of the 9 patients known to be symptom-free, one has been followed 1 year or less, 3 for 2 years, 1 for 3 years, and 4 have been followed for more than 6 years since the stoma was closed. One patient in the group has remained well for 17 years. Included in this group of symptom-free patients were 2 who had sigmoidovesical fistulas which were closed at the time that the stoma was established. It is evident that patients may remain free from symptoms of diverticulitis for prolonged periods without resection. However, in this series of cases, the satisfactory outcome was achieved with respect to less than one third of the patients who underwent closure without resection, and it would seem that it was impossible to predict with certainty before closure which patients will have symptoms subsequently.

Eleven of the 20 patients whose symptoms recurred had not undergone further surgery at the last report. The vesicosigmoidal fistula in 2 of the 11 cases had recurred, in one case after 1 year and in the other after 8 years. Four of the 11 patients had persistent fecal fistulas associated with recurrent attacks of inflammation, and 5 patients suffered from recurrent attacks of inflammation and obstruction. The remaining 9 patients had undergone further operative treatment at the time of the last report. A colonic stoma had been re-established in 1 case of the 9, a colonic stoma followed by resection of the involved sigmoid had been

carried out in 5 cases and, in 3 cases, subsequent attempts to close the stoma had been made, all of which had failed.

A conception of the disability and the serious condition that may follow closure of a colonic stoma, made with adequate indication, in treatment of complicated diverticulitis can be gained from review of the following case:

A physician, 47 years of age, had the first symptoms of diverticulitis 2 years before he was first seen at the clinic. At that time, an exploratory operation had been done because of lower abdominal tenderness and pain. A pelvic abscess due to perforating diverticulitis was found and appendectomy was done. Following this operation, a persistent external fecal fistula developed and the patient continued to have recurrent pelvic abscesses.

Approximately 2 years after this operation, a double-barreled colonic stoma, orad to the diverticulum, was established at the clinic and the pelvic abscesses were drained. Complete relief from all symptoms followed and the patient insisted that the stoma be closed in spite of advice to the contrary. At his request, also, the ventral hernia that resulted from the original operation was repaired about 6 weeks after the closure. Less than 3 months later, recurrence of the diverticulitis and development of another pelvic abscess necessitated the establishment of a second double-barreled colonic stoma. The patient was much relieved again but returned to the clinic 6 months later when, at his insistence, a second attempt was made to repair the ventral hernia. This operation was complicated by extensive infection of the body wall, which required drainage on several occasions. Three and a half years after establishment of the first stoma, and approximately 1 year after establishment of the second stoma, the patient was persuaded to submit to resection of the involved segment of sigmoid. An exteriorization type of operation was done. The resulting temporary stoma and the previously established colonic stoma were closed successfully and without complications within 18 weeks of the exteriorization operation.

In all, he was almost completely disabled for 6 years from the time of the first operation and he spent considerably more than half of this time in a hospital.

Resection of the involved segment of colon. The majority of patients in both series were subjected to some type of resection of the involved sigmoid. It is our feeling that when adequate indications exist for surgical interference, the safest procedure is to establish, orad to the lesion, a colonic stoma that completely diverts the fecal stream and then to allow sufficient time for the inflammatory reaction in and around the walls of the sigmoid to subside before attempting further surgery. Whether or not subsidence has occurred can be judged from proctoscopic and roentgenologic examination but, as a rule, 6 months to 1 year should elapse before resection is undertaken. Obviously, whenever serious suspicion of malignancy exists, the resection must be undertaken much earlier. The presence of extensive peridiverticulitis materially increases the risk of resection. From the present review, it would seem, also, that exteriorization operations are safer than procedures in which primary anastomoses are attempted.

Preliminary colonic stoma; subsequent exteriorization operation.—In series A, 22 patients were treated by means of a preliminary colonic stoma and a subsequent exteriorization operation. There were 3 hospital deaths in the group, a mortality rate of 14 per cent for the resection. Of the remaining 19 patients, 16 are well. Of the 3 remaining patients of the 19, 1 has continued to complain of pain in the region of the exteriorization operation and 1 committed suicide 2 years after the operation, presumably because of ill health. The final patient of the 3 died elsewhere of what was reported to be obstruction of the bowel 1 year after the resection.

In series B, 41 patients had an exteriorization type of resection following establishment of a colonic stoma. There were no deaths in this group.

Preliminary colonic stoma with subsequent end-to-end anastomosis.—In series A, 24 patients were treated by means of preliminary colonic stoma and subsequent resection with an end-to-end anastomosis. There were 4 deaths, a hospital mortality rate of 17 per cent for the resection. The colonic stomas of 3 patients who survived the operation were still open at the last report and 1 patient in the group has been lost track of. Fifteen of the 16 remaining patients are well and 1 patient has a persisting fecal fistula at the site of the resection but no other symptoms.

In series B this type of operative procedure was performed on 20 patients with 1 fatality.

Resection without preliminary colonic stoma.—There is a small group of cases of complicated diverticulitis in which it is relatively

safe to perform a primary resection and to unite the bowel by end-to-end anastomosis. The criteria of safety for such a procedure are: (1) There should be no evidence of obstruction. (2) The inflammatory process should be chronic or mildly subacute. (3) The involved segment of the bowel should be short, so that after resection the two cut ends of the bowel which are to be united are free of inflammatory infiltration. Safety will be further assured if, before closing the abdomen, a temporary colonic stoma is established in a loop of bowel orad to the site of resection.

Primary resection of the involved segment of colon was carried out in 98 cases in series A. An exteriorization type of operation was done in 76 cases, with 13 deaths in the hospital. Primary resection with end-to-end anastomosis was employed to treat 16 patients, with 2 deaths in hospital, and primary resection with side-to-side anastomosis was done in 2 cases without a fatality. In the 4 remaining cases, continuity of the bowel was not re-established and the patients were left with single-barreled colonic stomas. One of these patients died. The mortality rate of 16 per cent in these 98 cases compares favorably with the mortality rate of the two stage operation of preliminary colostomy and resection, which was 15 per cent. It is probable, however, that patients treated by primary resection had no obstruction and less extensive and less complicated diverticulitis than did those treated by means of preliminary colostomy and subsequent resection.

As mentioned above, primary resection without anastomosis was attempted in 4 cases; each of the patients was left with a single-barreled colonic stoma. The indication for this procedure usually was that the bowel was so shortened that neither an exteriorization operation nor primary anastomosis was thought feasible at the time of resection. One patient, as has been said, died following the operation, 1 patient subsequently underwent successful anastomosis between the sigmoid and the rectosigmoid, and 2 patients remained well but with the colonic stoma.

Now to cast back a few sentences to primary exteriorization operations. Results were comparable to those following other types of resection. Fifty of the 63 patients who survived the operation were entirely well and 9 others were well but had fecal fistulas at the site of the exteriorization. In 7 of these 9 cases one attempt at closure failed and in 2 of the 9 closure had not been attempted. Two patients of the 50 died of causes unrelated to their diverticulitis and 2 others complained of persisting pain in the region of the operative incision.

Fourteen patients survived the operation of primary resection with end-to-end anastomosis. Nine patients were well at the last report. Three had persisting fecal fistulas with attacks of inflammation. In 1 case of this group of 3 a colonic stoma was made subsequently and since then the patient has remained well, with the stoma. In the remaining 2 cases of the 14, strictures of the bowel developed at the site of the anastomosis. The late results following this type of resection were less satisfactory than those following other types of resection.

In series B, primary resection of the involved segment of sigmoid was carried out in 48 cases. An exteriorization type of resection was performed in 38 cases with 1 fatality. In 6 cases, primary resection of the sigmoid with end-to-end anastomosis was performed and, before closure of the abdomen, a temporary colonic stoma was established in a loop of bowel orad to the site of the resection. All the patients survived. Primary resection with end-to-end anastomosis without colostomy was carried out in 4 cases with 1 fatality.

Other operative procedures. In series A, other procedures were carried out rarely, usually because of unusual circumstances. In 2 cases, after preliminary colostomy, the involved segment of colon was resected and the ends above and below the resected portion were turned in and dropped back into the abdomen. One of the 2 patients died of pulmonary embolism and the other remained well, with the double-barreled stoma. Cecostomy in 2 cases, ileostomy and appendicostomy in 1 case each, were carried out for treatment of high grade obstruction. Three of the 4 patients died and the remaining patient recovered and required no further surgical treatment. Ileocolostomy was attempted in 3 cases with 1 death in hospital. One patient had recurrent partial ob-

TABLE III.—MISCELLANEOUS SURGICAL PROCEDURES CARRIED OUT AT MAYO CLINIC IN SOME OF THE CASES OF SERIES B

	Cases
Drainage of pelvic abscess	1
Closure of colonic stoma Stoma established elsewhere 4	6
Stoma followed resection of sigmoid elsewhere 2	
Colostomy and closure of jejunocolic fistula	1
Colostomy and repair of fistula	2
Colostomy, repair of fistula and closure of colonic stoma	4
Colostomy, resection of sigmoid, ileosigmoidostomy and partial colectomy	2

struction and 1 a persistent fecal fistula after this procedure. In 2 cases the sigmoid was simply wrapped in omentum. One of these 2 patients continued to have recurring attacks of diverticulitis, while the outcome in the other case is not known. In 3 cases, drainage of an abscess caused by diverticulitis was the only surgical procedure employed. The results in all 3 cases were poor. In 1 other case, the sigmoid was freed up and sutured to the body wall with no improvement in the symptoms.

Miscellaneous procedures which included resection, and which were employed in series B, are represented in Table III.

Mortality in series A and B compared. The surgical procedures employed and the mortality rates in the two series are shown in Table IV. In comparing the two series, the most noteworthy feature is the marked reduction in mortality rate in series B, to 4.2 per cent, together with a decided rise in the rate of resectability. Of the 245 patients in series A, resection of the involved segment of sigmoid was carried out in 146, or 60 per cent, whereas of the 144 patients in series B the bowel was resected in 111, or 77 per cent. The contrast between the two series is even more striking when the mortality rate in the cases in which resection was performed is compared. Of the 146 patients (8 from the miscellaneous group of Table IV) in series A who underwent resection, 24 died in hospital, a mortality rate of 16 per cent, whereas of the 111 patients in series B who underwent resection, 3 died, a mortality rate of 2.7 per cent.

TABLE IV.—SURGICAL PROCEDURES AND MORTALITY RATE

Surgical procedures	Series A: 1908–1940			Series B: 1941–1945		
	Patients	Deaths	Per cent	Patients	Deaths	Per cent
Colostomy only	38	6	15.8	12	1	8.3
Colostomy, subsequent closure	31	1	3.2	7	1	14.3
Colostomy, subsequent exteriorization	22	3	13.6	41	0	0
Primary exteriorization	76	13	17.1	38	1	2.6
Colostomy, subsequent resection and end-to-end union	24	4	16.7	20	1	5.0
Primary resection, end-to-end anastomosis and colostomy	0	0	0	6	0	0
Primary resection, end-to-end anastomosis. No colostomy	16	2	12.5	4	1	25.0
Miscellaneous	38	7	18.4	16	1	6.2
	245*	36	14.7	144	6	4.2

*As explained in the text (paragraph 3), there were actually 5 patients less than 245.

Of the 6 patients in series B who died, infection attributable to the operation was the cause of death in 3 cases. Infection of the abdominal wall developed in 2 cases following resection and in the third peritonitis developed 2 days following repair of a jejunocolic fistula that was caused by the crushing of the spur of a colostomy that had been performed elsewhere. The fourth patient of the 6 died of gangrenous cholecystitis following closure of a colonic stoma. The fifth patient a woman, 71 years old, whose intestine was acutely obstructed, died from bronchopneumonia 24 hours after colostomy. The sixth patient died of cerebral hemorrhage 14 days following an exteriorization operation and abdominal hysterectomy.

COMMENT

We are convinced that the improved results obtained in series B are definitely attributable to chemotherapy. Nevertheless, the two series of cases are not altogether comparable because, in the past 20 years, other changes in routine surgical management in all colonic cases may have influenced the results. A more

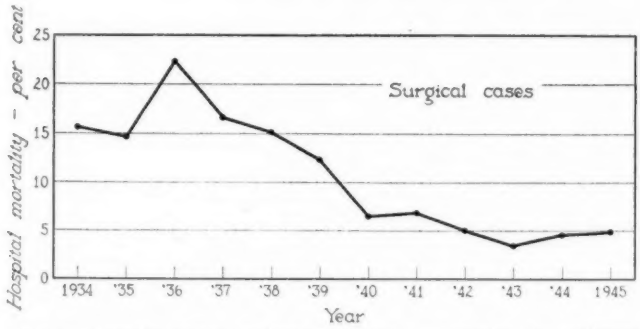

Fig. 1. Mortality among patients subjected to operation for malignant lesions of the large intestine and rectum, 1934–1945.

accurate appraisal of the value of chemotherapy in surgery of the colon could be obtained by comparing the results of two large series of colonic cases in which conditions were practically identical except that chemotherapy was employed in one series.

Since the organization of a special colon service in the Mayo Clinic nearly 20 years ago, all patients with lesions of the colon and rectum who are considered candidates for major surgical treatment have received preoperative treatment in the hospital for 3 to 5 days or longer, depending on the condition of the patient. The principal objectives of the treatment are: (1) to decompress and cleanse the large bowel; (2) to combat loss of blood and to establish and maintain protein balance by blood transfusions; (3) to combat dehydration by intravenous injection of saline and glucose solutions; (4) to establish and maintain concentration of vitamins, especially as regards vitamins C and K; (5) to combat potential infections by chemotherapy.

In the fall of 1939 we began using the sulfonamide compounds in colonic surgery. At first, perhaps because of the surgeon's innate skepticism concerning the value of drugs, especially any drug with such advance build-up as had been given to the sulfonamide compounds, 5 to 10 grams of the crystals were only occasionally placed in the peritoneal cavity prior to closure of the wound in those cases in which peritonitis was feared because of actual or suspected soiling. As experience enlarged, the surgeon slowly, and perhaps with reluctance, became convinced of the efficacy of the sulfonamide compounds and began to use them routinely. Since 1942, following the research of Poth, succinyl sulfathiazole (sulfasuxidine) has been given by mouth routinely as a preparatory measure, 12 to 15 grams daily over a period of 3 to 5 days. In recent years, after the supply of penicillin became readily available, this substance has been used frequently as an added measure of therapy. Other than the introduction of chemotherapy, there has been in the Mayo Clinic no major change in the management of colonic and rectal lesions during the past 12 years. Since, therefore, there was only one variable factor of importance in the management of patients during this period, it appeared worth while to compare the immediate surgical results in cases in which the patients had not had the benefit of chemotherapy with those in which the patients had received it. For this purpose, the yearly hospital mortality rate of all patients who had undergone any operation for carcinoma of the colon or rectum from 1934 to 1945 inclusive, was computed. As Figure 1 reveals, the mortality rate before 1939 varied between 15 and 20 per cent. A slight drop occurred in 1939, the year in which the sulfonamide compounds were first casually or intermittently used, and then, in 1940, there was a precipitous drop to around 5 per cent, where the rate has since remained.

In addition, the yearly surgical and resectability rates for the same 12 years were determined. The surgical rate is defined as the number of cases in which operation was performed divided by the total number of cases

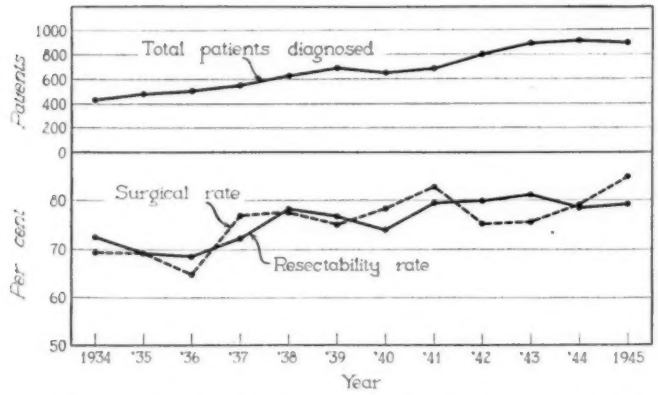

Fig. 2. Resectability rate of patients with malignant lesions of large intestine and rectum, 1934–1945.

in which a diagnosis of carcinoma of the colon or rectum was made. The resectability rate is the number of patients on whom resection was performed divided by the number of patients on whom operation was performed. As indicated in Figure 2, there has not been a decline either in the surgical rate or in the rate of resectability during the years of decline in mortality; instead, there has been an appreciable rise.

Finally, in order to determine the influence of the factor of infection on the hospital mortality rate, the cause of death of all patients in this series was tabulated. Since peritonitis and pneumonia are unequivocably infections, it seemed pertinent to compare the incidence of these two complications as a cause of death in those cases in which the patient had received little or no sulfonamide compound with those in which the patient had received adequate dosage of sulfonamide. As indicated in Figure 3, the mortality rate in each category decreased as the years passed.

The changes that have occurred in surgery of the colon since the introduction of chemotherapy have been as spectacular and revolutionary as the changes wrought by iodine therapy in surgery of exophthalmic goiter. The analogy is striking. In the preiodine era of thyroid surgery for exophthalmic goiter, technical perfection of the surgical procedure of partial thyroidectomy was no definite assurance that the patient would endure the operation, for not infrequently severe hyperthyroid crisis would supervene, resulting in fatal issue. Likewise, in the era of colonic surgery before chemotherapy was available, technically errorless resection of a segment of bowel was not definite assurance that the patient would survive, for not infrequently infection would spread to produce fatal peritonitis. The surgeon who worked in each field after resorting to refinements of technique and other measures, finally learned that the best means of combating the hidden danger (acute hyperthyroidism in the one and spread of infection in the other) was to divide the operation into stages. In both fields, employment of stage procedures resulted in marked improvement but only partially eliminated the hidden dangers peculiar to each. Thus it was only after preoperative iodine therapy had been standardized that the surgeon could be reasonably assured that, barring some accident, his patient with exophthalmic goiter would endure an uncomplicated partial thyroidectomy in one stage. And so, in the field of colonic surgery, only in recent years, since the advent of chemotherapy, could the surgeon be reasonably confident that his patient with a lesion of the colon or rectum would survive an uncomplicated resection of the colon. Finally, as the statistical data obtained in the preiodine era were not a sound basis for appraisal of modern thyroid surgery, so the results in the era before chemotherapy

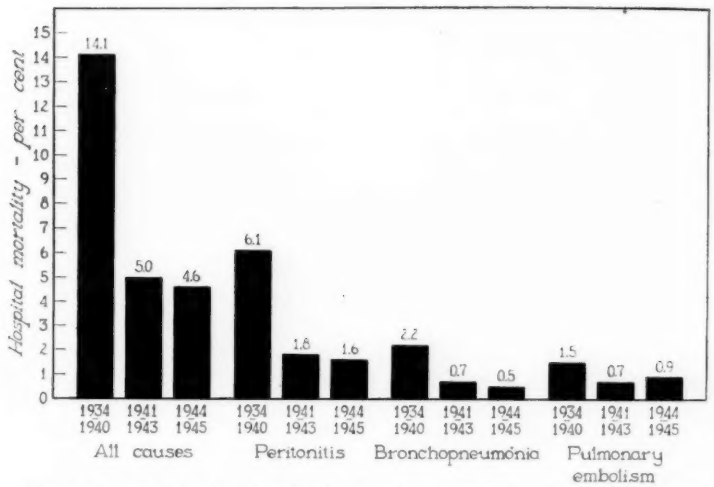

Fig. 3. Causes of death. Mortality from various causes of death following operations for malignant lesions of the colon and rectum, 1934–1945.

are not a fair basis for judging modern colonic surgery. Although iodine and chemotherapy each has markedly reduced the incidence of the most dangerous complication in its respective field, it must be strongly emphasized that both forms of therapy must be considered bs extremely valuable adjuncts to surgery put by no means as substitutes for the proved principles of sound surgery.

The marked reduction in the hospital mortality rate associated with the surgical treatment of diverticulitis suggests that the indications for surgical treatment should probably be broadened. As indicated previously, there is general agreement that uncomplicated diverticulitis should be managed conservatively and that surgical treatment should be advised only if complications have developed. Nonsurgical treatment has definite limitations. It cannot be relied on to bring about complete subsidence of the inflammatory process, nor to prevent development of complications which will require operation, nor even to free the patient from his symptoms. It follows that in many cases under nonsurgical management, the patient has some disability and there is always the possibility of the subsequent development of complications which will require operation. Furthermore, as we have demonstrated, the safest type of operative treatment for complicated diverticulitis is the establishment of a colonic stoma orad to the inflammatory segment of bowel, followed by resection of the involved segment after many months of the patient's living with his colonic stoma. Both the reluctance to advise surgical treatment and the choice of staged operations in the past are readily understandable in view of the former mortality rate of approximately 15 per cent. With a reduction of the mortality rate to about 4 per cent, the proposal that operations should be advised for less complicated diverticulitis may be seriously entertained. It is probable, as well, that the surgical mortality rate could be reduced even further if patients with less extensive disease were operated on, and certainly a greater number of single stage procedures and even resections with primary anastomoses could be carried out safely. The advantage of removal of the involved segment of bowel, with subsequent cure of the patient, is evident when the uncertainty associated with nonsurgical management is considered.

SUMMARY

While the great majority of patients suffering from diverticulitis of the sigmoid portion of the colon respond satisfactorily to nonsurgical management, the complications of per-

foration, obstruction, and fistula usually require operation. Surgical exploration, and frequently resection of the involved segment of colon, are indicated at times because of the impossibility of distinguishing with certainty between carcinoma and diverticulitis. In the present series, carcinoma could not be excluded with certainty in about 25 per cent of the cases in which a preoperative diagnosis was ventured.

Local excision of an inflamed diverticulum, or local excision of a fistula and closure of the wall of the bowel was possible rarely, but was followed by unsatisfactory results in approximately half of the cases in which it was attempted.

The establishment of a colonic stoma orad to the lesion was associated with a hospital mortality rate of 5.1 per cent in those cases in which treatment was given in the era before chemotherapy was available and with a rate of 1.1 per cent in those cases in which chemotherapy was employed. Excluding a small group of patients who died essentially of pelvic abscess and infection, a large percentage of the patients with a colonic stoma orad to the lesion remained clinically well as long as the stoma was maintained. Of the patients whose stomas were closed and resection of the bowel was not done, only about a third remained well. Results following closure of the stoma without previous resection of the involved segment of bowel were so unsatisfactory that we are of the opinion that, as a rule, resection should be done in all cases unless proof can be established of complete subsidence of the inflammatory process.

The safest plan of treatment proved to be establishment of a colonic stoma orad to the lesion followed, after an interval of 6 to 12 months, by an exteriorization type of resection. Resections of this type were associated with a hospital mortality rate of 13.6 per cent in the era before chemotherapy but there were no deaths after chemotherapy became available. The results after both primary resection and following resections done after establishment of a colonic stoma were satisfactory in that approximately 80 per cent of the patients were cured. The results were less satisfactory in the group of patients who underwent primary resection with end-to-end anastomosis of the bowel.

The employment of modern chemotherapy in the surgical management of complicated diverticulitis of the sigmoid has partially eliminated the occurrence of serious infections and thereby has been the major factor in the marked reduction of the surgical mortality rate from 14.7 per cent to 4.2 per cent.

With the risk of operation so markedly reduced and in view of the obvious advantage of resection, serious consideration can be given to broadening the indications for surgical treatment for diverticulitis.

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METHODS FOR DIFFERENTIAL DIAGNOSIS OF PAINLESS JAUNDICE

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MUCH has appeared in the recent literature concerning the differential diagnosis of surgical jaundice (1, 3, 5, 7, 8, 11). We are presenting here a few simple, practical methods for this differential diagnosis based on clinical and laboratory data of a type practicable even by those with limited laboratory facilities. Many of the recent articles stress the use of complex laboratory examinations which require highly skilled and specially trained technicians. The tests herein included can be performed in any ordinary laboratory and have been exact enough to enable accurate diagnosis 98 per cent of the time.

Painful jaundice is almost always due to stones and therefore presents little in the way of a diagnostic problem though occasionally, hepatitis may cause confusion. Painless jaundice, however, presents a somewhat complex diagnostic problem due to the great group of hepatitides. This diagnostic problem is simplified if one is familiar with the normal physiology of bile pigments and with the basic abnormal physiology of the various types of jaundice, and, in addition, makes use of the common basic laboratory tests required for the differential diagnosis of painless jaundice.

In Figure 1 is seen the normal physiology of bile pigments (2). Bilirubin I designates that form of bilirubin which has not entered the liver cell and bilirubin II represents that form of bilirubin which is either in or which has passed through the liver cell. Also from the diagram one sees how urobilinogen is formed by a process of reduction of bilirubin II in the intestine. Urobilinogen is then excreted in part in the feces and reabsorbed in part by the portal blood. Normally the reabsorbed pigment is practically all re-excreted in the bile. The junction of the arrow to the kidney with the arrow of reabsorption indicates the passage of urobilinogen into the blood and its excretion by the kidney when urobilinogen is presented to the liver faster than the liver is able to reconvert it to bilirubin II.

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The physicochemical properties of bilirubin I and bilirubin II are of importance as a basis for the understanding of certain laboratory data. Bilirubin I is a colloidal compound which is readily oxidized and passes slowly into the tissues with the result that high concentrations are necessary before clinical jaundice is manifest. Bilirubin I is insoluble in water and Ehrlich's solution but is soluble in alcohol. Bilirubin II is also a colloidal compound but is combined with bile salts. It is slowly oxidized and passes readily into the tissues and is therefore visible at lower levels than is bilirubin I. Bilirubin II is soluble in water, Ehrlich's solution, and in alcohol.

The common basic laboratory tests required for the differential diagnosis of jaundice are: (1) Van den Bergh reaction, (2) Pettenkoffer test, (3) Hay's test, (4) Gmelin's test, (5) foam test, (6) galactose tolerance test. All of these tests are required and should be used in conjunction with other clinical data.

The Van den Bergh reaction, a modification of Ehrlich's diazoreaction, is employed for the detection of bile pigments in the blood serum. There are two main types of the reaction based upon whether the bile pigment has or has not passed through the liver cell. The direct reaction occurs with bilirubin II and is chemically possible because of the solubility of the substance. One cubic centimeter of Ehrlich's solution is added to 1 cubic centimeter of serum and within 30 seconds a violet diazobilirubin is formed. The indirect reaction occurs with bilirubin I and is also based upon its solubility. One cubic centimeter of serum plus 2 cubic centimeters of 95 per cent alcohol plus Ehrlich's solution results in a reddish

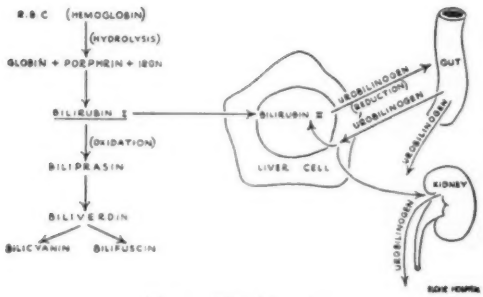

Fig. 1. Bile pigments.

violet color developing immediately. The direct reaction is usually indicative of obstructive jaundice or some condition in which bilirubin II is present in the blood stream. There are two subreactions under the direct type; namely, the delayed direct and the biphasic reaction which usually indicate a jaundice due to liver damage. The indirect reaction due to bilirubin I is commonly seen in hemolytic jaundice and collections of old blood. Normal serum will also give the indirect reaction. All sera which give the direct test will also give the indirect test. The indirect test is used as a quantitative measure of serum bilirubin. When the bile salt concentration in the blood is elevated, a direct test results because bilirubin II is formed when bile salts are added to normal serum.

The Pettenkoffer test for bile salts is performed by adding 10 per cent cane sugar solution plus 2 drops of concentrated sulfuric acid to 5 cubic centimeters of the fluid to be tested. If bile salts are present, a red ring will form at the junction of the solutions. The red colored ring is due to cholalic acid.

The Hay's test depends upon the phenomena of lowered surface tension which is produced by the bile salts. This action is due to the fact that bile salts act as "wetting agents." Flowers of sulfur are added to the solution to be tested and sink immediately when the urine contains over 0.5 milligram per cent of bile salts. They sink with agitation in the range between 0.0025 and 0.5 milligram per cent. In solution containing less than 0.0025 milligram per cent the flowers of sulfur will float in spite of agitation. This test is the basis of a quantitative determination of bile salts in the urine (13).

The Gmelin's test is used to detect bile in the urine. The fluid to be tested is passed through a moistened filter paper to which is added 1 drop of fuming nitric acid which oxidizes pigments resulting in a series of colored rings—yellow, red, green, violet.

The foam test is the most simply conducted for the detection of bile in the urine. It consists of a greenish foam forming over the solution when it is shaken. This action is also based on a lowered surface tension.

The icteric index is of no additional value when the quantitative Van den Bergh reaction is used and therefore merits no discussion.

Another test of considerable value is the galactose tolerance test which is based upon the principle that galactose is not converted to glucose by the liver when considerable damage is present. Because this is only a rough test of liver function and considerable liver damage must be present before the test is impaired, it lends itself admirably to the purpose. This test consists of giving 40 grams of galactose and checking the urinary excretion. In the normal patient less than 3 grams will be excreted in the urine in a 5 hour period. In jaundice due to or with severe liver damage, the amount of excretion will vary from 4 to 6 grams in 5 hours depending upon the degree of liver impairment.

The final important laboratory test is the Schmidt's test for the detection of urobilin concentration in the stools. The stool is incubated for 24 hours with Ehrlich's reagent and a quantitative estimation is then made of the diazobilirubin resulting. If the concentration is below 5 to 10 milligrams, the test is said to be negative; if it is above, it is positive. The presence of urobilin in the stool of course indicates that bile is getting into the intestinal tract to form urobilinogen (9, 13, 15). Urobilinogen in urine may be detected by a similar method but without incubation. Watson has recently described a semiquantitative method for urobilinogen in stool and urine which may be used (9, 15).

The basic examinations for diagnosis in a given case are therefore first conducted on the urine to determine the presence or absence of

bile and urobilinogen; on the stool to determine the quantitative amount of urobilin; on the blood to determine the size, shape, number, and character of the red blood cells, the quantitative amount of bilirubin in the serum, and the type of Van den Bergh reaction obtained. The galactose liver function test is then carried out to determine the degree of impairment present.

In the nonobstructive type of jaundice, the abnormal physiology is briefly that bilirubin I is formed more rapidly than the liver can convert it into bilirubin II. This occurs in three abnormal physiologic states.

The first of these states is the condition in which the liver is normal but the blood cell destruction is markedly increased. The clinical examples of this group are the so-called "acholuric jaundice," congenital hemolytic icterus and toxic hemolytic icterus. The results of the basic examinations for this type of physiologic disturbance are based upon a high bilirubin I content in the blood. The Van den Bergh reaction is indirect and of variable quantity, usually rather high. The urine contains no bile nor bile salts but has an increased urobilinogen content; the stool will show a positive Schmidt's test and the galactose tolerance will be less than 3 grams in 5 hours, indicating normal function of the liver.

The second state is that in which the liver is moderately impaired and the blood cell destruction moderately increased. The clinical representatives of this group are black water fever and pernicious anemia. Examination of the urine and stool show findings similar to the first state; also the Van den Bergh reaction, both quantitative and qualitative, will be similar. The diagnostic differences will be found in examination of the red blood cells and by an impaired galactose tolerance, approximately 4 grams excretion in 5 hours.

The third state in which this occurs is that seen when the liver is severely impaired and the red blood cell destruction remains normal. This is clinically seen theoretically in severe terminal cirrhosis. The diagnostic laboratory finding is a markedly impaired galactose tolerance test, usually around 6 grams excreted in 5 hours. The values for the quantitative Van den Bergh will usually be considerably lower than in the other two states but may terminally closely approximate them.

Several other points in the differential diagnosis of nonobstructive jaundice are of the utmost importance (1, 5, 7). In hemolytic icterus the signs of increased bone marrow activity are present; there is an anemia if the breakdown of red blood cells is more rapid than the bone marrow can supply cells with a normal hemoglobin content. In the congenital form of hemolytic icterus, the red cells are spherocytic, are more fragile than normal, and the serum contains an elevated specific hemolysin titer. In the toxic hemolytic icterus, the specific hemolysin titer and the cell fragility are normal. The diagnosis of jaundice occurring in pernicious anemia and thrombopenic puerpera is corroborated by the other clinical signs, by the symptoms, and by the laboratory findings of the diseases.

Obstructive jaundice is divided into two classes based on the site of the obstruction, namely, intrahepatic and extrahepatic.

Intrahepatic obstructive jaundice results from a diffuse hepatitis (4, 10, 14) which causes edematous occlusion of the small bile canaliculi of the liver. The effect of such occlusion is partially to obstruct the ducts in the same manner as the stone in the extrahepatic system. Bile pigments pile up behind the obstruction and result in an increase of the obstruction. Intrahepatic obstructive jaundice is always incomplete. The etiology of such jaundice may be divided into six groups: (1) Viral—"catarrhal" jaundice usually follows an upper respiratory infection in a young adult and is of approximately 30 days' duration. It is characterized by progressive jaundice for about 21 days followed by rapid regression in about 10 days. (2) Drugs—the widespread use of sulfonamides both externally and intraperitoneally is responsible for this type. It is usually seen with massive overdose of the drug such as results from intraperitoneal implantation in the presence of a partially impaired liver. The halogen derivatives may also be responsible for this type of jaundice, anesthetic agents and hypnotics being the most frequent causative agents. (3) Bacterial—this is most commonly the re-

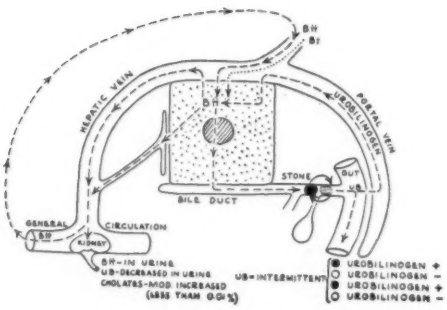

Fig. 2. Bile pigment circulation; incomplete obstruction (stone).

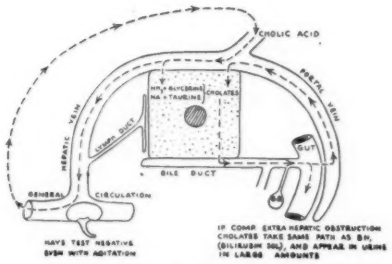

Fig. 3. Diagram showing normal bile salt circulation.

sult of a diffuse ascending cholangitis. (4) Spirochetal—Weil's disease with its two causative organisms, icterohemorrhagica and canicola, is the example of this. (5) Neoplasm—diffuse primary neoplasms of the liver are rare and therefore an unlikely cause but metastatic neoplasms or diffuse leucemic infiltrations may result in such a picture. (6) Hepatic congestive heart failure if severe and longstanding may produce this type of jaundice.

The Van den Bergh reaction in intrahepatic obstructive jaundice is indirect early due to an increase of bilirubin I pigments but it later changes to a delayed direct or biphasic reaction. The urine has bile, and bile salts may be increased. The urobilinogen content is increased (12) or normal. Schmidt's test on the stool vary from day to day due to the variation in the degree of obstruction of the bile canaliculi. The average case will show a sequence as follows: 3 or 4 positive reactions, 1 negative reaction, 2 more positive reactions, another negative reaction. There is an impairment in galactose tolerance with a resultant excretion of 4 to 5 grams in 5 hour period.

Extrahepatic obstructive jaundice may be due to stones, strictures, or neoplasms located in the hepatic ducts, the common hepatic ducts, the common duct, or the ampulla. If complete obstruction is present in extrahepatic jaundice, there is a 95 per cent chance that the cause is a neoplasm either in the common duct, ampulla or head of the pancreas. Such a case has only a 5 per cent chance of being a stone. In a case with incomplete obstruction, the chances are that 95 per cent of the time a stone is the etiological agent; in 5 per cent of such cases, a neoplastic obstruction may be the cause (15). Neoplastic obstruction of this type is usually due to direct extension from a carcinoma of the stomach or colon. The primary question in diagnosing this type of jaundice is—"Is the obstruction complete or incomplete?" To determine this point, we must again fall back on our laboratory studies. The Van den Bergh reaction in both cases will be immediate direct but the amount of bilirubin in the incomplete obstruction is usually below 10 milligrams per cent whereas in the complete, it is generally above 10 milligrams per cent. In the complete, the Schmidt's tests on the stools will be consistently negative; in the incomplete, they will vary from positive to negative depending upon the position of the obstruction. Examination of the urine in both cases will reveal bile but there will be absolutely no urobilinogen in the urine in the complete obstruction. The urobilinogen will vary from day to day in the incomplete types.

Figures 2, 3, 4, 5 represent in diagrammatic form, the normal and altered physiology of the bile pigments and the bile salts in complete and incomplete obstruction. The diagrams are self-explanatory, the arrows representing the course of the pigments and bile salts under normal and abnormal conditions. It can be seen in the diagrams that the conjugation of the bile salts in the liver cell is dependent upon the available glycine.

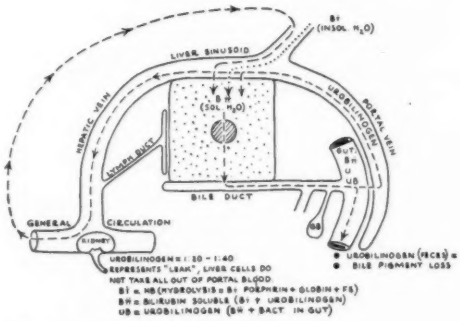

Fig. 4. Normal circulation; bile pigment.

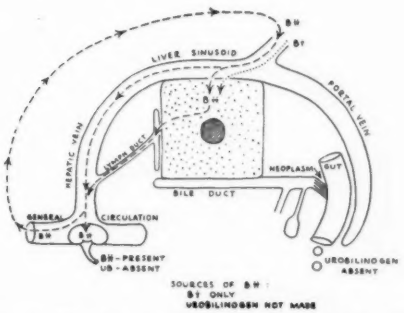

Fig. 5. Bile pigment circulation; complete obstruction (neoplasm).

In conclusion the pertinent data from 5 recent ward cases are presented together with the completed scheme of differential diagnosis in each case. In each of these cases the diagnosis was verified by operation or postmortem examination.

CASE 1. Painless jaundice of 2 weeks' duration, liver palpable and smooth, soft palpable spleen, urine negative for bile, positive for urobilinogen 1/120, Schmidt's positive 4 times, Van den Bergh delayed direct, serum bilirubin 2.8 milligrams per cent, hemoglobin 8 grams, red blood cells 3.00 with many small irregularly formed cells, fragility test normal, normal hemolysin titer, galactose tolerance test 3 grams in 5 hours.

The primary diagnosis in this case is nonobstructive jaundice. Next, the physiologic group in nonobstructive jaundice which best fits this case must be determined. Since the galactose test is normal, it can be assumed that the liver is functioning satisfactorily. This case therefore falls into the group with a normal liver but increased red blood cell destruction rate. The causes of this type of jaundice are: (1) hemolytic icterus which may be divided into two types: congenital—with the high titer of specific hemolysin and the fragile red cell; toxic with the normal red cell and hemolysin titer; (2) hemosiderosis may be diagnosed by taking a skin biopsy and staining for the Prussian blue reaction; (3) pernicious anemia may be diagnosed by the blood picture, bone marrow smears, and response to treatment. The most likely diagnosis in this case is, therefore, toxic hemolytic icterus.

CASE 2. Painless jaundice of 5 days' duration, liver large, soft and tender, spleen not palpable, heart and lungs normal, urine positive for bile and urobilinogen in dilutions of 1/60, Schmidt's positive 5 times, direct Van den Bergh, serum bilirubin 8 milligrams per cent, red blood cells 3.75, hemoglobin 60 per cent, galactose tolerance 5 grams in 5 hours.

The primary diagnosis of this case is obstructive jaundice. The physiologic group is determined by the presence of bile in the stool and is obviously the "incomplete." Next we must determine whether this incomplete jaundice is extrahepatic or intrahepatic in origin. Since the galactose test shows impairment, indicative of liver damage, we can assume that the jaundice is of intrahepatic origin. The most likely diagnosis is, therefore, incomplete intrahepatic obstructive jaundice, that is, hepatitis.

CASE 3. Painless jaundice of 2 weeks' duration, moderate dyspepsia, small palpable mass in midline above the umbilicus, urine positive for bile and urobilinogen 1/40 dilution, Schmidt's 1 minus and 3 pluses, 4 plus occult blood in stools, Van den Bergh direct, serum bilirubin 8 milligrams per cent, red blood cells 3.75, hemoglobin 60 per cent, galactose tolerance test 3 grams in 5 hours; x-ray films showed absent peristalsis in pyloric region of stomach.

The primary diagnosis of Case 3 is obstructive jaundice. The physiologic group determined by the presence of bile in the stool is the "incomplete." Since the galactose test is normal, we assume this jaundice to be of extrahepatic origin. Because it is extrahepatic, there is 95 per cent chance of it being a stone and 5 per cent chance of it being a neoplasm involving the duct system in some way. In view of the occult blood, the palpable mass and the persistent pyloric x-ray defect, the diagnosis of an extrahepatic incomplete obstructive jaundice due to carcinoma of the stomach with secondary involvement and obstruction of the right hepatic duct was made and verified by autopsy.

CASE 4. Painless jaundice for 5 days' duration, hematemesis 2 times, liver and spleen not palpable, urine negative for bile, contained urobilinogen 1/160 dilution, Schmidt's test positive 3 times, Van den Bergh direct, serum bilirubin 5 milligrams per cent, red blood cells 2.60, hemoglobin 40 per cent, galactose tolerance test 5 grams in 5 hours, normal fragility test and platelet count.

The primary diagnosis of Case 4 is nonobstructive jaundice. The physiologic group as determined by an impaired galactose test and a normal fragility test is that group with the impaired liver and normal red blood destruction rate. The cause of this type of

jaundice is usually a severe terminal portal cirrhosis. The diagnosis in this case was, therefore, terminal portal cirrhosis in atrophic phase with esophageal varices. The direct Van den Bergh reaction resulted in this case from an increased concentration of bile salts in the blood stream due to failure of the impaired liver to handle the bile salt circulation properly.

CASE 5. Painless jaundice of 3 weeks' duration, liver and spleen not palpable, urine positive for bile 4 times, negative for urobilinogen, stool negative for bile 6 times, Van den Bergh direct, serum bilirubin 17 milligrams per cent, urine grossly bloody on one occasion, cystoscopic and pylogram examination negative except for trigonitis, galactose tolerance test 3 grams in 5 hours.

The primary diagnosis in this case is obstructive jaundice. The physiologic group as determined by the presence of bile in the urine and the absence of bile in the stool is therefore the "complete." The galactose tolerance test is normal; therefore this is a case of extrahepatic complete obstructive jaundice and has a 95 per cent chance of being a neoplasm involving the duct system and a 5 per cent chance of being a stone. The urinary bleeding ceased upon the administration of vitamin K. Subsequent operation and biopsy proved the lesion to be carcinoma of the lower third of the common bile duct.

SUMMARY

A simplified method for diagnosis of jaundice based on common easily performed laboratory examinations is presented together with several cases to illustrate how the method may be applied to a given case.

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EDITORIAL

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OCTOBER, 1947

RADIATION INJURIES

INJURIES incurred by physicians working with the roentgen rays or radium in the early days were so much publicized that nearly every case was known and discussed. Nowadays, with the greatly augmented number of physicians and assistants administering x-ray therapy and participating in x-ray diagnostic work, the much larger percentage of injuries sustained remain almost unheralded. The importance of recognizing and avoiding these dangers from irradiation is not given sufficient emphasis. Surgeons can testify to the increasing number of physicians and dentists for whom they are called upon to repair irradiation damage to hands, and yet these injuries include only a part of the extensive category of damages which radium and x-rays may cause.

The surgeon who employs the fluoroscope as an aid in the removal of foreign bodies or in the adjustment of mal-apposed fractured bones, unless especially trained in radiology, subjects himself and his colleagues, as well as the patient, to danger of dermal injury, to say nothing of systemic damage to the blood-making organs and especially of damage to the leucocytes. We find physicians, even specialists in radiology, who have suffered as a result of self-administered irradiation. The writer recalls very well a surgeon who treated his own hand with radium, with resulting irreparable radium injury, malignant degeneration, and finally miserable death from pulmonary metastases. Another well-known radiologist of vast experience permitted himself to continue to assist in the adjustment of fractured bones and in the removal of foreign bodies under x-ray control until his own hands developed advanced skin damage, with subsequent malignant degeneration and fatal pulmonary metastases. The young physician, just graduated from medical school and interneship, who succumbs to the importunities of the salesman of x-ray equipment and buys his own fluoroscope for use in his office, may yield to the temptation to use the x-rays in fluoroscopic management of fractures or foreign bodies. Unless he takes proper precautions he is likely, within a couple of years, to suffer such damage to his hands that he will need extensive plastic surgery with replacement of skin of the injured members. Even veterans in radiology who have always used leaded gloves and palpating spoons often find themselves with degenerating skin damage requiring plastic surgery in order to save their lives, to say nothing of relieving the constant pain caused by the chronic x-ray injuries.

It is possible to make reasonably safe use of the x-rays for all of these purposes. For the removal of foreign bodies under the fluoro-

scope an accumulated time of 10 minutes at 3 milliamperes will emit the maximum radiation which should be utilized in any given case, and no one, surgeon or radiologist, should participate in such operations any oftener than occasionally, certainly not routinely.

There are numerous ways of accomplishing satisfactory removal of foreign bodies by other than fluoroscopic means; in fact, it is now often possible to substitute for potentially dangerous x-ray methods the use of electronic or telephonic foreign body finders. Radiologists should be among the first to urge the adoption of these non-radiological methods because they offer a means of by-passing the danger inherent in the x-ray method.

Every piece of diagnostic equipment used for fluoroscopy should have a built-in protecting filter of 1.0 millimeter of aluminum or its equivalent, and under no circumstances should this be removed. The size of the field of illumination on the screen should be reduced to the very minimum. Long-handled forceps should be employed. The image of the bones of the hands of the operator or radiologist should never be seen on the fluoroscopic screen. The roentgen tube should never be activated even for a second unless the observer's eyes are focused upon the screen ready for instant observation, and in no case should the apparatus be excited until after the observer's eyes have been thoroughly adapted to the dark.

The insiduous character of the dangers resulting from small repeated exposures to x-ray and radium is one important explanation of failure to take protective precautions. The direct injury to the cellular structure of the surface of the hands is usually not evident until months or even years after exposure.

It has been said that the three most important protective devices for the operation of x-ray equipment and for the use of radium are training, common sense and experience, and the most frequent causes of injury are carelessness and ignorance. We are told that between 1919 and 1935 there were seen at the Mayo Clinic 135 physicians with x-ray injuries, of whom 91 contracted their injuries during fluoroscopic fracture reduction. Of these 78 admitted failure to take protective precautions, and 11 confessed that they began the use of protective gloves only after sustaining the injury.

The foregoing remarks relate principally to damage to the hands, but other systemic dangers threaten the radiologist. These dangers are all the more threatening to the physician who owns x-ray equipment and without adequate training undertakes to use it occasionally, especially for fluoroscopic work. No one can suppose for a moment that fluoroscopy gives adequate information except in a rather limited field, as, for instance, in the examination of the chest.

The fluoroscope shows the excursion and the relative height of the phrenic cupolas, the condition of the phrenic angles, the mobility of the heart in relation to the diaphragm, the esophagus, and gross lesions of the chest. It is impossible for even the most expert and the most experienced to see as much tissue detail in the fluoroscope as can be seen on the films. The fluoroscope can never take the place of the films; it does, however, supplement the film study in an indispensable manner. Fluoroscopy gives information as regards the size of the heart and the movements of the walls of the different chambers of the heart. The pulsations of the aorta and of vascular tumors can be studied and differential diagnosis made in some cases; although the absence of pulsations does not mean that a certain shadow is not due to a vascular tumor, and the presence of a pulsation does not mean that the tumor is of the aorta. Transmitted pulsations are dif-

ficult to differentiate from intrinsic pulsations.

It might be assumed that radiologists are so conscious of the hazards of their specialty that they do not need to be reminded of these dangers, but a survey of forty-five hospitals[1] showed that both radiologists and technicians receive considerably more radiation during fluoroscopy than they were aware of. These exposures were the most excessive noted in the survey. Cutaneous effects varying from atrophy of the skin to the formation of epithelioma were noted in 20 per cent of the radiologists seen in the hospitals of this survey.

The remedy for this deplorable frequency of x-ray damage lies in education. The radiologist should know better; others, such as general surgeons and especially gynecologists, urologists, and dermatologists, as well as dentists, should make a special study of radiation physics before attempting to employ x-ray apparatus or radioactive substances.

JAMES T. CASE

[1]Scheele, L. A., and Cowie, D. B. J. Am. M. Ass., 1941, 117: 588-591.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

AN excellent and concise review of the author's long experience following scrotal circulation studies and surgical treatment of varicoceles with symptoms is presented in *Varicocele semiologia y cirugia* by Bernardi.[1] The author credits Ivanissevich with correcting misconceptions and teachings of previous writers in regard to the venous circulation of the male genital organs. By the use of phlebography the author was able to show for the first time the anastomosis of the anterior and posterior venous systems in cases of large varicoceles. The anatomy, the return venous circulation, and the preoperative and postoperative results are very well illustrated in this volume.

Under semeiology of varicocele the author discusses scrotal elongation, scrotal measurement, recognition of the posterior venous ectasia, palpatory maneuver for the anteroposterior venous communication, recognition of the spermatic artery, and palpatory classification of varicoceles.

The author carefully reviews the anatomy of the inguinal canal and finds its average length only 2 to 3 centimeters rather than 4 to 5 centimeters and the internal orifice of the canal is usually found 1 centimeter above the crural arch. A 3 to 4 centimeter skin incision beginning a fingerwidth above the external inguinal ring is described. The external oblique is incised and by palpation the internal ring may be recognized beneath the aponeurosis. The technique of opening the tunica fibrosa, identification and division of the internal spermatic vein and all its associated trunks are well described in detail. Venous trunks, no matter how small, should not be overlooked at the time of operation. Abdominal pressure may distend and help visualize the smallest veins by reflux.

The author states that ligation of the spermatic trunks at the internal orifice of the inguinal canal constitutes a direct and causal treatment of varicocele. Section and ligation produce a slow and progressive reduction of the dilated vessels with absolute disappearance of the reflux. If reflux persists the patient is not cured in the strict medical sense even though the symptoms have been improved. Bernardi sincerely believes that no other procedure is capable of providing at one and the same time so high a percentage of cures and greater simplicity and security in its execution, with such absolute respect for the spermatic artery and the gland, as the one mentioned in this compendium.

This volume is an excellent reference covering all the newer concepts of simple varicoceles. The surgical technique for division of the inguinal spermatic vein is well illustrated and described.

LEANDER W. RIBA.

THE well-known treatise on endocrinology that first appeared in 1941, *Essentials of Endocrinology*[2] by Grollman, has been revised and largely brought up to date. The current edition is characterized by the same excellent features that were widely recognized when the book first appeared. It is made up of a systematic discussion of each of the recognized endocrine glands in their anatomical, physiological, chemical, patholigical, and clinical aspects. The author has been primarily concerned, it would appear, to produce a book that would be useful to clinicians, though it is also valuable for laboratory investigators. It is probable that only the latter will have much occasion to take issue with the author, and the disagreements will be few and mostly of no great moment.

Less than justice has been done to recent brilliant studies of the thyrotropic hormone and its influence on the intimate enzymatic processes in the thyroid gland as brought out by such students as Dempsey, Salter, and Chaikoff. The newer work utilizing radioactive iodine as a tracer substance is also inadequately considered. The older work of Cannon on the emergency function of the adrenal medulla is again dismissed with a perfunctory nod. The cortex of the adrenal fares little better. Grollman still persists in the now rather unique opinion that this structure forms but a single hormone despite the fact, which he cites, that at least three categories of effects of cortical deficiency are clearly evident and that active fractions of cortical extract are known selectively to influence these processes. The important adaptive function of the adrenal cortex in relation to stresses is inadequately treated as is that structure as an accessory sex organ. Throughout the book an occasional impatient *ipse dixit* is substituted for adequate judicial consideration of evidence on moot issues. The discussion of the pineal gland is a case in point. Another feature that is annoying, at least to those readers who are interested in the "who's who" aspect of the subject, is the common relegation of the names of authorities cited to the bibliographies.

One of the unique features of the book is an especially good interpolated chapter on the hypothalmus

[1] VARICOCELE SEMIOLOGIA Y CIRUGIA. By Dr. Ricardo Bernardi. Buenos Aires: Libreria "El Ateneo" Editorial, 1947.

[2] ESSENTIALS OF ENDOCRINOLOGY. By Arthur Grollman, Ph.D., M.D., F.A.C.P. 2nd ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

in relation to clinical disorders that suggest, but have not been shown to be, endocrinopathies. The possibility was overlooked, however, that these disorders may be due to hypothalmic influences transmitted humorally to the anterior pituitary, as Long has suggested, in relation to thyrotropin discharge.

In format the book is attractive. The illustrations are nearly all well selected and a considerable proportion of them are original. The proofreading has been notably competent. So logically has it been organized, and so adequate are the headings, that the vast wealth of incorporated material is easily accessible. Altogether, the book is recommended as one of the best in this difficult field. ROY G. HOSKINS.

IN a book of 416 pages entitled *Synopsis of Operative Surgery*,[1] the author, H. E. Mobley, presents surgical procedures covering all systems and regions of the body. There are many illustrations, most of which are of the schematic form used in older texts. The descriptions are oversimplified, and lacking in detail necessary for students or less experienced surgeons. There is, however, much useful information and many worth while helpful suggestions.

RUSSELL T. BOTHE.

THE well prepared monograph *Penicillin Therapy*[2] by John A. Kolmer is a very timely contribution for the practicing physician as well as the medical and surgical specialist in an era characterized by such rapid advances in the field of chemotherapy. The author has reviewed the voluminous literature on this subject and has concisely summarized the most important contributions which have been made. The book is largely written from a clinical standpoint and the major portion of it is concerned with the clinical phases of practical penicillin therapy, including the available methods and routes of administration. Other chapters deal with the history, production, methods of assay, and properties of penicillin and streptomycin.

Detailed descriptions of the methods for measuring the concentration of chemotherapeutic agents in the various body fluids and for determining bacterial susceptibility should be very valuable to the medical technician. The established principles of therapy with penicillin, streptomycin, and other antibiotics are discussed. In summarizing the experiences of others, the author often quotes conflicting viewpoints which may tend to confuse the reader somewhat, although a detailed and acceptable plan of treatment is always given for each disease. The book is well arranged, adequately illustrated, and well edited. Each chapter is followed by a complete annotated bibliography. It should be valuable not only as a reference book, but also as a practical guide to effective chemotherapy. W. A. ALTEMEIER.

[1] SYNOPSIS OF OPERATIVE SURGERY. By H. E. Mobley, M.D., F.A.C.S. 2nd ed. St. Louis: The C. V. Mosby Co., 1947.

[2] PENICILLIN THERAPY; INCLUDING STREPTOMYCIN, TYROTHRICIN, AND OTHER ANTIBIOTIC THERAPY. By John A. Kolmer, M.S., M.D., Dr. P.H., Sc.D., LL.D., L.H.D., F.A.C.P. 2nd ed. New York, London: Appleton-Century Co., 1947.

THE author of *Dr. Samuel Guthrie; Discoverer of Chloroform*[3] had prepared a short paper about the almost forgotten discoverer of chloroform and thought it worthwhile to bring together what little was known about this man and his work. The resulting small volume depicts Dr. Samuel Guthrie as a pioneer physician and a scientific investigator of unusual intelligence and of varied interests.

Footnotes and collateral notes, placed at the end, add items of interest to the story. In the appendix are reproduced a few family papers and several papers from the *American Journal of Science and Arts*, 1831–1832, which contains all of the contributions of Dr. Guthrie. Numerous illustrations are included.

This attractive book will be enjoyed by those interested in the history of anesthesia, the development of firearms, and in the life in remote settlements of a century ago. MARY FRANCES POE.

FOR the past few years it has been increasingly difficult for the practicing physician as well as all other scientists who are not working in the field of blood grouping and blood antibodies to keep abreast of the literature and the developments related to the new Rh blood type, and to know what information is really factual and which papers are theoretical and often merely confusing. A good review of the subject, and particularly of the literature, is therefore a great help to any physician, and especially to surgeons who may run into difficulties with transfusions and to obstetricians who may encounter Rh incompatibility as a serious complication of otherwise normal gestation.

The new review by Edith Potter[4] fills an important need in medicine. It offers a comprehensive review of the literature up until November, 1946, and in general separates the good from the bad in this very much confused field. The chapters on pathology, clinical diagnosis, and course of the disease, and the illustrations in the book are particularly worth referring to. The details of postmortem examinations of babies suffering from hemolytic disease of the newborn cannot be found in as complete and clear fashion in any other monograph or book on this subject. This volume can therefore be recommended to all readers of SURGERY, GYNECOLOGY AND OBSTETRICS without reservations regarding it. LOUIS K. DIAMOND.

THE seventh edition of Buchanan's *Manual of Anatomy*[5] is the American form of the guide which first appeared in 1906. The original work was written by A. M. Buchanan, Professor of Anatomy in Anderson's College, Glasgow. The current revision is the fourth in the edited series, and the first done by Professor F. Wood Jones and five of his colleagues at the University of Manchester.

[3] DR. SAMUEL GUTHRIE; DISCOVERER OF CHLOROFORM. By J. R. Pawling. Watertown, N.Y.: The Brewster Press, 1947.

[4] RH. . . ITS RELATION TO CONGENITAL HEMOLYTIC DISEASE AND TO INTRAGROUP TRANSFUSION REACTIONS. By Edith L. Potter, M.D., Ph.D. Chicago: The Year Book Publishers, Inc., 1947.

[5] BUCHANAN'S MANUAL OF ANATOMY. 7th ed. Edited by F. Wood Jones, D.Sc. (Lond., Adelaide, Melb.), M.Sc. (Manch.), M.B., B.S. (Lond.), F.R.S., F.R.C.S. (Eng.). Baltimore: Williams & Wilkins Co. 1946.

The opening chapter deals very helpfully with terminology and topography, the second with development and growth, the third through the sixth with skeletal anatomy. The next six chapters are arranged on regional basis; they present the gross structure of the upper extremity, lower extremity, abdomen, thorax, head and neck. These regional accounts are followed by three sections on the nervous system and the organs of special sense. A serviceable glossary follows, the latter succeeded by the terminal section on biography—offering notes on anatomists whose names appear eponymously in the manual's text.

The regular chapters (i.e., the text material exclusive of glossary, notes, and index) cover more than 1500 pages. They present amply all of the expected information on gross anatomic structure. However, the treatment of musculature does not equal that by the late Professor Bardeen in the Jackson edition of the *Morris*; the account of the vascular system suffers by comparison with that by Professor Patten in Schaeffer's edition of *Morris' Human Anatomy*. Altogether, the text of the Cunningham *Manual* (likewise regional in pattern) outranks that of Buchanan's *Manual*.

The book is illustrated with 847 uncolored figures prepared from simple line drawings, and 48 roentgenograms. Some of the line drawings, deleted from predecessor editions, have been restored; 180 new drawings of similar character were borrowed from Professor Jones' volumes on the hand and foot. In the preface, these drawings are described as being "beautiful" as well as "clear." That they possess clarity is uncontestable; however, were a reviewer carelessly to admit that these illustrations are beautiful, he would be obliged to employ artificially laudatory terms in describing the eminently better figures of Cunningham's *Text-Book and Manual*, those which used to appear in the excellent German editions of the Spalteholz and the figures which illuminated Sobotta-McMurrich *Atlas*. The pictures of bones—always undramatic—are adequate. The drawings of the muscles are generally satisfactory, although those depicting the deep antibrachial muscles, the fascial coverings and compartments of the palm, the synovial sheaths of the extensor tendons, the interossei, the hamstrings, and the anterior crural muscles are of the sort that one would expect to find in any ordinary compendium. The portrayal of perineal anatomy is not only poor, but incorrect; the pictorial treatment of the inguinal region is stylized, as is that of abdominal, pelvic, and thoracic viscera.

The only essentially new features are the x-ray plates. The text is standard, the numerous drawings conventional; the legends are not highly descriptive. However, despite the fact that the volume does nothing novel, and discharges its pedagogic obligation without use of distinctive text or of an exceptional series of figures, it might prove a desirable adjunct to a student's or a practitioner's library.

BARRY ANSON.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE DEVELOPMENT OF MODERN MEDICINE; AN INTERPRETATION OF THE SOCIAL AND SCIENTIFIC FACTORS INVOLVED. By Richard Harrison Shryock. New York: Alfred A. Knopf, 1947.

CHIRURGIE FONCTIONNELLE GYNÉCOLOGIQUE. By R. Bourg. Paris: Masson & Cie, Editeurs; Liege: Editions Desoer, 1947.

ANATOMIA QUIRURGICA DEL NERVIO FACIAL. By Vicente J. Bertola. Argentina: Imprenta de la Universidad Cordoba, 1947.

BONE DYSTROPHIES; A SYSTEMATIC REVIEW AND CORRELATION. By F. Y. Khoo. Chengtu, China: The Canadian Mission Press, 1945.

LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Hans Guggisberg. Basel: Verlag Von S. Karger, 1947.

PREOPERATIVE AND POSTOPERATIVE CARE. By William J. Tourish, M.D., F.A.C.S., and Frederick B. Wagner, Jr., M.D. Philadelphia: F. A. Davis Co., 1947.

CANCER GENITAL E GRAVIDEZ. By Prof. Dr. Jorge De Rezende. Buenos Aires: Secretaria Del Congreso, 1946.

CANCER GENITAL Y EMBARAZO. By Dr. Enrique Thwaites Lastra and Dr. Alfredo Jakob. Buenos Aires: Secretaria Del Congreso, 1946.

MAY'S MANUAL OF THE DISEASES OF THE EYE. By Charles A. Perera, M.D. Baltimore: Williams & Wilkins Co., 1947.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. Cameron, C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C. 6th ed. Philadelphia, Toronto: The Blakiston Co., 1947.

HOSPITAL CARE IN THE UNITED STATES. By the Commission on Hospital Care. New York: The Commonwealth Fund, 1947.

ENDOCRINOLOGY OF NEOPLASTIC DISEASES. A Symposium by Eighteen Authors. Edited by Gray H. Twombly, M.D., and George T. Pack, M.D. New York: Oxford University Press, 1947.

PATHOLOGY OF LABOR, THE PUERPERIUM AND THE NEWBORN. By Charles O. McCormick, A.B., M.D., F.A.C.S. 2nd ed. St. Louis: The C. V. Mosby Co., 1947.

A HANDBOOK FOR THE DIAGNOSIS OF CANCER OF THE UTERUS BY THE USE OF VAGINAL SMEARS. By Olive Gates, M.D., and Shields Warren, M.D. Cambridge, Massachusetts: Harvard University Press, 1947.

RENEWAL PAGES FOR THE LOOSE LEAF SPECIALTIES IN MEDICAL PRACTICE. Vols. 1 and 2. New York, Edinburgh: Thomas Nelson & Sons, 1947.

ERKRANKUNGEN DES UROPOETISCHEN SYSTEMS UND DER PROSTATA DURCH STORUNG DER BLUTSTROMUNG. By Professor Dr. Karl Hutter. Austria: Wilhelm Maudruch; New York: Grune & Stratton, Inc., 1947.